A Randomized Trial of Brimonidine Versus Timolol in Preserving Visual Function: Results From the Low-pressure Glaucoma Treatment Study

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• PURPOSE: To compare the alpha2-adrenergic agonist brimonidine tartrate 0.2% to the beta-adrenergic antagonist timolol maleate 0.5% in preserving visual function in low-pressure glaucoma.

• DESIGN: Randomized, double-masked, multicenter clinical trial.

• METHODS: Exclusion criteria included untreated intraocular pressure (IOP) >21 mm Hg, visual field mean deviation worse than −16 decibels, or contraindications to study medications. Both eyes received twice-daily monotherapy randomized in blocks of 7 (4 brimonidine to 3 timolol). Standard automated perimetry and tonometry were performed at 4-month intervals. Main outcome measure was field progression in either eye, defined as the same 3 or more points with a negative slope ≥ -1 dB/year at $P < 5\%$, on 3 consecutive tests, assessed by pointwise linear regression. Secondary outcome measures were progression based on glaucoma change probability maps (GCPM) of pattern deviation and the 3-omitting method for pointwise linear regression.

• RESULTS: Ninety-nine patients were randomized to brimonidine and 79 to timolol. Mean (± SE) months of follow-up for all patients was 30.0 ± 2. Statistically fewer brimonidine-treated patients (9, 9.1%) had visual field progression by pointwise linear regression than timolol-treated patients (31, 39.2%, log-rank 12.4, $P =$ .001). Mean treated IOP was similar for brimonidine- and timolol-treated patients at all time points. More brimonidine-treated (28, 28.3%) than timolol-treated (9, 11.4%) patients discontinued study participation because of drug-related adverse events ($P = .008$). Similar differences in progression were observed when analyzed by GCPM and the 3-omitting method.

• CONCLUSION: Low-pressure glaucoma patients treated with brimonidine 0.2% who do not develop ocular allergy are less likely to have field progression than patients treated with timolol 0.5%. (Am J Ophthalmol 2011;151: 671–681. © 2011 by Elsevier Inc. All rights reserved.)

O PEN-ANGLE GLAUCOMA IS A SLOWLY PROGRESsive neurodegeneration of retinal ganglion cells (RGCs) and their axons[1] characterized by a specific pattern of optic nerve head and visual field damage.[2] Low-pressure (normal-tension) glaucoma is a clinical term often used to describe patients with open-angle glaucoma in whom the measured untreated intraocular pressure (IOP) is always within a statistically normal range.[3] While any separation between normal and abnormally elevated IOP is intrinsically arbitrary, population-based studies demonstrate that low-pressure glaucoma represents 20% to 39% of patients with open-angle glaucoma in the United States and Europe.[4–6]

The pathophysiologic mechanisms of glaucomatous neurodegeneration are incompletely understood. Elevated IOP is the most important known risk factor for disease onset and progression that is amenable to modification. Multicenter clinical trials confirm the value of reducing IOP in patients with ocular hypertension,[7] open-angle glaucoma with elevated IOP,[8,9] and low-pressure glaucoma.[6,10] However, many patients continue to experience disease progression despite IOP reduction.[6,7,9,11]

Laboratory studies have demonstrated that alpha2-adrenergic agonists are neuroprotective in experimental optic nerve injury, models of glaucoma, ischemia-induced injury, and photoreceptor degeneration.[12] Yet clinical trials in nonglaucomatous diseases such as nonarteritic anterior ischemic optic neuropathy, Leber hereditary optic neuropathy, and retinal dystrophies have failed to show treatment benefit with alpha2-adrenergic agonist use.[12] We performed a 4-year double-masked, randomized, multicenter clinical trial of the efficacy of monotherapy with brimonidine tartrate 0.2% vs timolol maleate 0.5% eye drops, medications with equal IOP-lowering efficacy,[13,14] in preventing or delaying visual field progression in patients with low-pressure glaucoma.
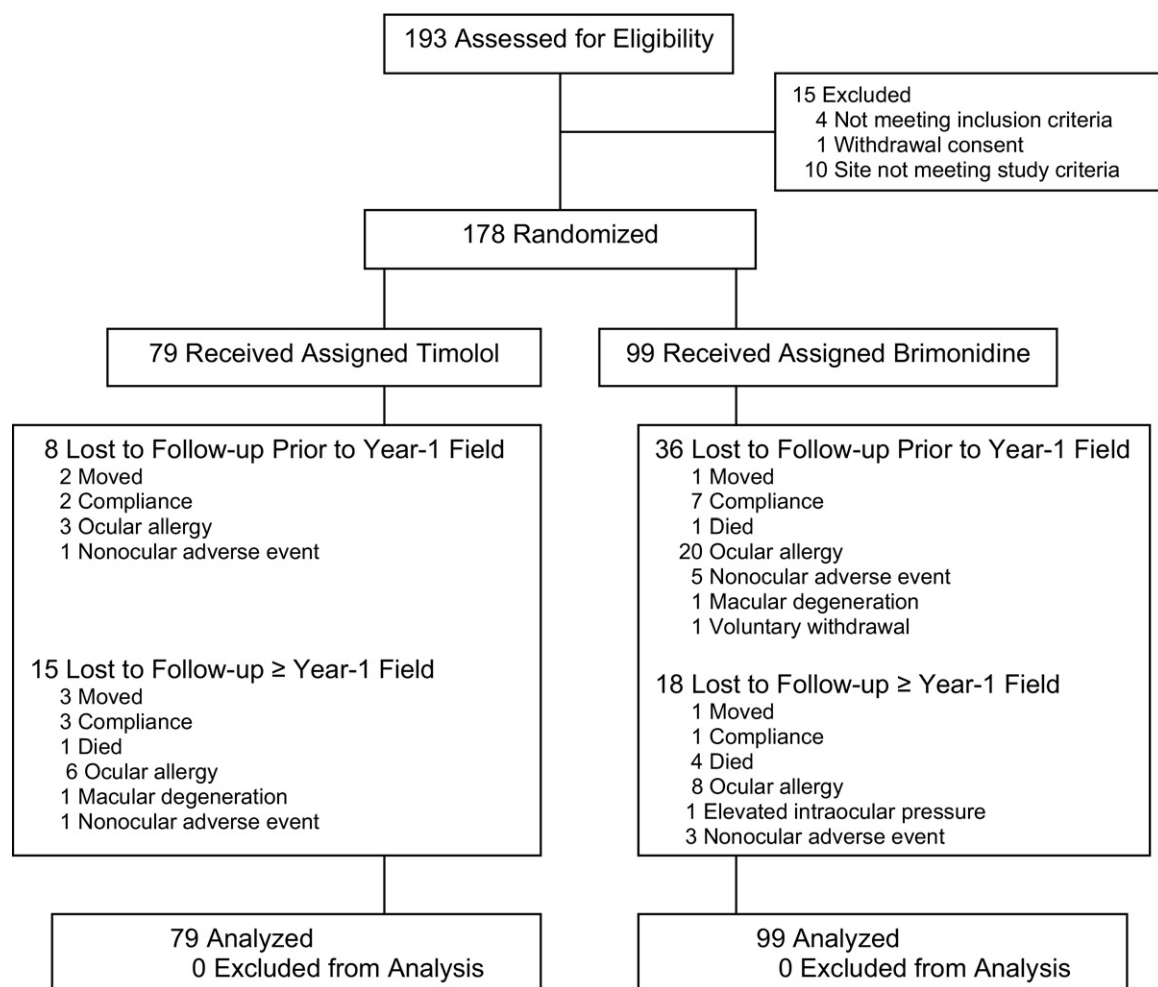
FIGURE 1. Flowchart of participant progress in the Low-tension Glaucoma Treatment Study. Patients lost to follow-up and who discontinued intervention are separated according to completion of the year-1 visual field. 193 patients were screened. 3 patients were screening failures and 190 patients were randomized. 12 randomized patients were subsequently excluded (10 from withdraw of a study site, 1 withdrew consent, and 1 did not meet entry criteria).

METHODS

METHODS ARE FULLY DESCRIBED ELSEWHERE.[15]

• INCLUSION AND EXCLUSION CRITERIA: Study patients had previously diagnosed low-pressure glaucoma that fulfilled the following eligibility criteria: all known untreated IOP ≤21 mm Hg, open iridocorneal angles by gonioscopy, at least 2 reproducible visual fields with glaucomatous defects in 1 or both eyes on automated perimetry (Humphrey Field Analyzer; Carl Zeiss Meditec, Inc, Dublin, California, USA) with the location of the field defect consistent with the photographic appearance of the optic nerve head, and age ≥30 years. To determine eligibility based on IOP, all patients receiving IOP-lowering treatment underwent a 4-week washout without therapy. Baseline IOP (measured with a calibrated Goldmann applanation tonometer) had to be ≤21 mm Hg in both eyes with <5 mm Hg difference between the eyes on a diurnal curve (8:00 AM, 10:00 AM, noon, 4:00 PM) assessed prior to randomization.

Ocular exclusion criteria included the following: a history of IOP >21 mm Hg in the patient record, best-corrected visual acuity worse than 20/40 in either eye, a history of angle closure or an occludable angle by gonioscopy, prior glaucoma incisional surgery, inflammatory eye disease, prior ocular trauma, diabetic retinopathy or other diseases capable of causing visual field loss or optic nerve deterioration, extensive glaucomatous visual field damage with a mean deviation worse than −16 decibels (dB), or a clinically determined threat to central fixation in either eye. Systemic exclusion criteria included a resting pulse <50 beats/minute; severe or uncontrolled cardiovascular, renal, or pulmonary disease that would preclude safe administration of a topical beta-adrenergic antagonist; and a prior myocardial infarction or stroke. Continuation of systemic medications that could affect IOP was allowed as long as the doses remained constant throughout the trial.

• RANDOMIZATION, TREATMENT, AND MASKING: Patients were randomly assigned to receive monotherapy with either brimonidine tartrate 0.2% containing 0.005% (50 ppm) benzalkonium chloride (Alphagan; Allergan, Inc, Irvine, California, USA) or timolol maleate 0.5% containing 0.01% (100 ppm) benzalkonium chloride (Timoptic; Merck & Co, West Point, Pennsylvania, USA) twice daily in both eyes, including the morning before each visit. To allow for higher patient attrition in the brimonidine group attributable to an expected rate of adverse events of approximately 20%,[13,16] randomization and delivery of medications (provided by Allergan, Inc) to the sites were stratified in blocks of 7 (4 brimonidine to 3 timolol). The randomization list was maintained and masked study medications were provided in new 10-mL white bottles labeled with the assigned randomization number directly to the clinical centers by an independent pharmacy (Fountain Valley Cancer Center Pharmacy, Fountain Valley, California, USA). Ocular treatment other than the study medication was not permitted. Investigators, patients, and the visual field reading and coordinating centers were all masked to patient assignment.

Endpoints requiring discontinuation from the study included: treated IOP >21 mm Hg that was repeated within 1 month, safety concern as judged by the treating physician, symptomatic ocular allergic adverse events (hyperemia, pruritus, stinging, and/or conjunctival folliculosis) requiring medication cessation, retinal events that could alter visual acuity or visual field (eg, age-related macular degeneration), the occurrence of systemic (eg, respiratory or cardiovascular) adverse events that prevented the administration of topical timolol, nonocular intolerable events associated with topical brimonidine (eg, xerostomia, fatigue, drowsiness), or if the patient moved or declined continued participation. Collection of data from discontinued patients ceased at their final study visit. Data up to this point were included in the analysis, but discontinued patients were no longer followed as part of the study.

• STUDY VISITS: Patients were examined at 1 and 4 months after initiation of treatment. Subsequent visits were at 4-month (± 2 weeks) intervals. Pre- and post-randomization morning visits recorded the following: ocular and systemic history, blood pressure, pulse, corrected visual acuity, IOP, slit-lamp examination, and optic disc evaluation for cup-to-disc ratio and the presence or absence of disc hemorrhage. Gonioscopy and stereoscopic optic disc photographs were performed annually. Full-threshold standard achromatic perimetry (Humphrey 24-2) visual field was performed at 4-month intervals throughout the study according to protocol guidelines.

• OUTCOME MEASURES: The primary outcome measure was visual field progression in either eye as determined by pointwise linear regression analysis of all study visual fields

TABLE 1. Patient Baseline Characteristics in the Low-pressure Glaucoma Treatment Study

	Brimonidine (n = 99)	Timolol (n = 79)	P Value[a]
Sex, male/female	44/55	31/48	.48
Age, mean (SD) years	64.3 (10.9)	65.7 (10.4)	.28
Diurnal IOP, mean (SD) mm Hg	15.8 (2.1)	15.2 (2.4)	.13
Visual field, mean (SD) dB			
Mean deviation	−5.3 (3.5)	−4.8 (3.0)	.32
Pattern standard deviation	5.9 (3.0)	5.8 (2.4)	.86
Unilateral field loss, patients (%)	27 (27.3)	21 (26.6)	>.99
Visual acuity (Snellen decimal fraction)	0.89 (0.2)	0.90 (0.2)	.74
Refraction spherical equivalent	−0.70 (2.2)	−0.54 (2.5)	.61
Corneal thickness, mean (SD) μm	540 (30)	547 (36)	.18
New glaucoma diagnosis, patients (%)	24 (24.2)	20 (25.3)	1.00
Blood pressure, mean (SD) mm Hg			
Systolic	130 (17)	123 (17)	.41
Diastolic	76 (10)	76 (10)	.81
Diastolic ≤60 mm Hg, number (%)	8 (8.1)	6 (7.6)	1.00
First-degree history glaucoma (%)	30 (30.3)	28 (35.4)	.52
Ocular hypotensive therapy, patients (%)			
None	41 (41.4)	27 (34.2)	.35
Timolol	45 (45.5)	38 (48.1)	.76
Brimonidine	10 (10.1)	13 (16.4)	.26
Systemic disorders, patients (%)			
Migraine	6 (6.1)	3 (3.8)	.73
Diabetes mellitus	10 (10.1)	5 (6.3)	.43
Hypertension	41 (41.4)	36 (45.6)	.65
Systemic medications, patients (%)			
Beta-adrenergic antagonist	15 (15.2)	10 (12.6)	.67
Calcium channel blocker	14 (14.1)	16 (20.2)	.32
Alpha-adrenergic agonist	2 (2.0)	3 (3.8)	.66
Angiotensin converting enzyme inhibitor	23 (23.2)	16 (20.2)	.72
Statins	15 (15.2)	14 (17.7)	.69

[a]P values for comparison of baseline parameters for the brimonidine and the timolol groups: Mann-Whitney U test and Fisher exact test for categorical variables. Ocular measurements based on the mean of patient eyes.

FIGURE 2. Kaplan-Meier plot of the cumulative probability of developing visual field progression by Progressor analysis for the randomization groups in the Low-pressure Glaucoma Treatment Study. The numbers of active patients at risk and the number of patients developing visual field progression are presented at each 4-month period. Inactive (discontinued) patients and those reaching study end without field progression are withdrawn from the interval after their last completed visit.

with Progressor software (Medisoft Inc., Leeds, UK).[17,18] Visual field analysis was performed by an independent reading center (Devers Eye Institute, Legacy Health System, Portland, Oregon, USA) masked to the treatment assignment. Linear regression of the sensitivity (in dB) was performed at each test location to obtain the rate of change at that location, based on all fields up to and including the current examination. Default Progressor criteria were used to define a significant negative slope (worse than −1 dB/year for inner points and −2 dB/year for edge points) at the $P < 5\%$ level. Edge points for the Humphrey 24-2 field included the 2 outer nasal locations, 1 above and 1 below the horizontal. Criteria for visual field progression required confirmation at the next 2 examinations (ie, 4 and 8 months later) of a significant negative slope at the same 3 or more test locations. Therefore, the earliest that field progression could be detected was the month-16 examination (8 months to calculate the pointwise linear regression for the negative slopes and months 12 and 16 for confirmation). Progression criteria did not require the progressing locations to be contiguous.

A secondary outcome was visual field progression in either eye evaluated by Humphrey glaucoma change prob-

ability maps (GCPM). The GCPM[19] was based on pattern deviation maps rather than the total deviation plot used in the glaucoma change probability software to eliminate change caused by generalized depression of the visual field (eg, cataract). Progression by GCPM was defined as a significant worsening at $P < 5\%$ for the same 3 or more test locations that were confirmed at the next 2 examinations.[20] Progressing locations did not have to be contiguous.

To verify the results of the primary Progressor outcome measure, a post hoc analysis was performed using a 3-omitting method for pointwise linear regression[21,22] that used the default Progressor software criteria. This method was reported during the study and increases specificity by requiring that progression must be confirmed at 2 further visits when omitting from the series the visual field that caused progression to be suspected.

• STATISTICAL ANALYSIS: Pre-study sample size calculations indicated that 64 subjects would be required in each treatment arm to have an 80% power to detect a difference in visual field progression (at $\alpha = .05$ by 2-tailed test) based on the following assumptions: 1) a 4-year progression

	Brimonidine No. (%)	Timolol No. (%)	P
Randomized	99 (100)	79 (100)	
Discontinued prior to year 1	36 (36.4)	8 (10.1)	<.001[d]
Discontinued ≥year 1	18 (18.2)	15 (19.0)	
Progressor analysis[a]			Log-rank[e]
Visual field progression	9 (9.1)	31 (39.2)	12.4, <.001
Trial end without progression	36 (36.4)	25 (31.6)	
Glaucoma change probability maps[b]			22.0, <.001
Visual field progression	8 (8.1)	35 (44.3)	
Trial end without progression	37 (37.4)	24 (30.4)	
3-omitting method[c]			9.5, <.002
Visual field progression	5 (5.0)	21 (26.6)	
Trial end without progression	40 (40.4)	36 (45.6)	

[a]Progressor pointwise linear regression analysis.
[b]Humphrey glaucoma change probability maps (GCPM) using pattern deviation.
[c]The 3-omitting method for pointwise linear regression analysis using the default Progressor software criteria.
[d]Fisher 2-tailed test.
[e]Log-rank, visual field progression seen in significantly fewer patients assigned to brimonidine than to timolol.

rate of 30% in the brimonidine group and 55% in the timolol group[17]; 2) an attrition rate of 25%; and 3) 20% of subjects having only 1 eye eligible. Patients were analyzed in the group to which they were randomized. Analysis was patient-based and the event time to field progression was defined based on progression in either eye. The log-rank test was used to compare the time to field progression between treatment groups. Point estimates of proportion of subjects progressing were derived from Kaplan-Meier analysis, with standard errors from Greenwood's formula. Univariate comparisons between treatment groups were nonparametric (Mann-Whitney U test, Wilcoxon signed rank test) and the Fisher exact test for categorical variables. Reported values are mean ± SD and P values separately in the 2 arms are 2-sided. Statistical significance was defined as $P < .05$.

RESULTS

RECRUITMENT[15] WAS BETWEEN APRIL 28, 1998 AND JUNE 19, 2000, with 193 individuals assessed for enrollment (Figure 1). A total of 178 randomized participants were followed: 99 (55.6%) were allocated to brimonidine and 79 (44.4%) to timolol. There were no significant differences at baseline in demographics, ocular parameters, or systemic factors between the 2 treatment groups (Table 1).

Statistically more subjects assigned to brimonidine (36/99, 36.4%) dropped out prior to the year-1 examination than assigned to timolol (8/79, 10.1%) ($P = .001$, see Figure 1). The most common reason for discontinuation before the year-1 examination was localized ocular allergy that necessitated discontinuing the study medication in 20 of the 99 (20.2%) brimonidine and 3 of the 79 (3.8%) timolol subjects ($P = .001$). There were no statistically significant baseline differences between patients discontinued prior to the year-1 and patients completing the year-1 and later study visits within either treatment randomization group. Eleven brimonidine patients (11.1%) and 1 timolol patient (1.3%) dropped out prior to the first treatment visual field at month 4 ($P = .013$).

Mean (± SE) months of follow-up for all patients was 30.0 ± 1.2 (range, 3.2–50.2; 95% confidence interval [CI], 27.5–32.4) and in patients completing the year-1 study visit (n = 134) was 35.6 ± 1.0 (range, 11.5–50.2; 95% CI, 33.5–37.7). Baseline characteristics for the 63 of 99 (63.6%) brimonidine and the 71 of 79 (89.9%) timolol patients completing the year-1 visit were not significantly different between the 2 groups except for IOP, which was statistically higher ($P = .031$) in the brimonidine (16.2 ± 1.9) compared to the timolol patients (15.3 ± 2.4). An additional 18 brimonidine (8 of 99 with ocular allergy, 8.1%) and 15 timolol (6 of 79 with ocular allergy, 7.6%) patients were discontinued at or after the year-1 study visit (see Figure 1). For active patients, there were no missed visits (ie, visual field examinations) with subsequent 4-month follow-up examinations.

Six patients died during the study, 5 (5.0%) assigned to brimonidine and 1 (1.3%) to timolol, from causes unrelated to the study medications (see Figure 1). Causes for the 5 brimonidine patients were trauma, myocardial infarction (n = 2), pulmonary embolism, and complications following bowel surgery. The cause of death in the timolol patient was complications following bowel surgery.

A visual field endpoint for the pointwise linear regression primary outcome measure (Figure 2) was reached in significantly (log-rank 12.4, $P = .001$) fewer patients assigned to brimonidine (n = 9, estimate ± standard error = 10 ± 4%) than to timolol (n = 31, 33 ± 6%) (Table 2). Positive slopes (sensitivity increasing >1 dB/yr) on the same 3 or more test locations, not necessarily contiguous, on 3 consecutive fields were used to calculate the false-positive rate. There was no statistical difference in the frequency of significantly positive slopes in the 2 treatment groups: 9 patients assigned to brimonidine (8 reaching study end and 1 discontinued after year 1) and 8 patients to timolol (7 reaching study end and 1 discontinued after year 1). Two patients assigned to brimonidine and 1 to timolol who had field progression (significant
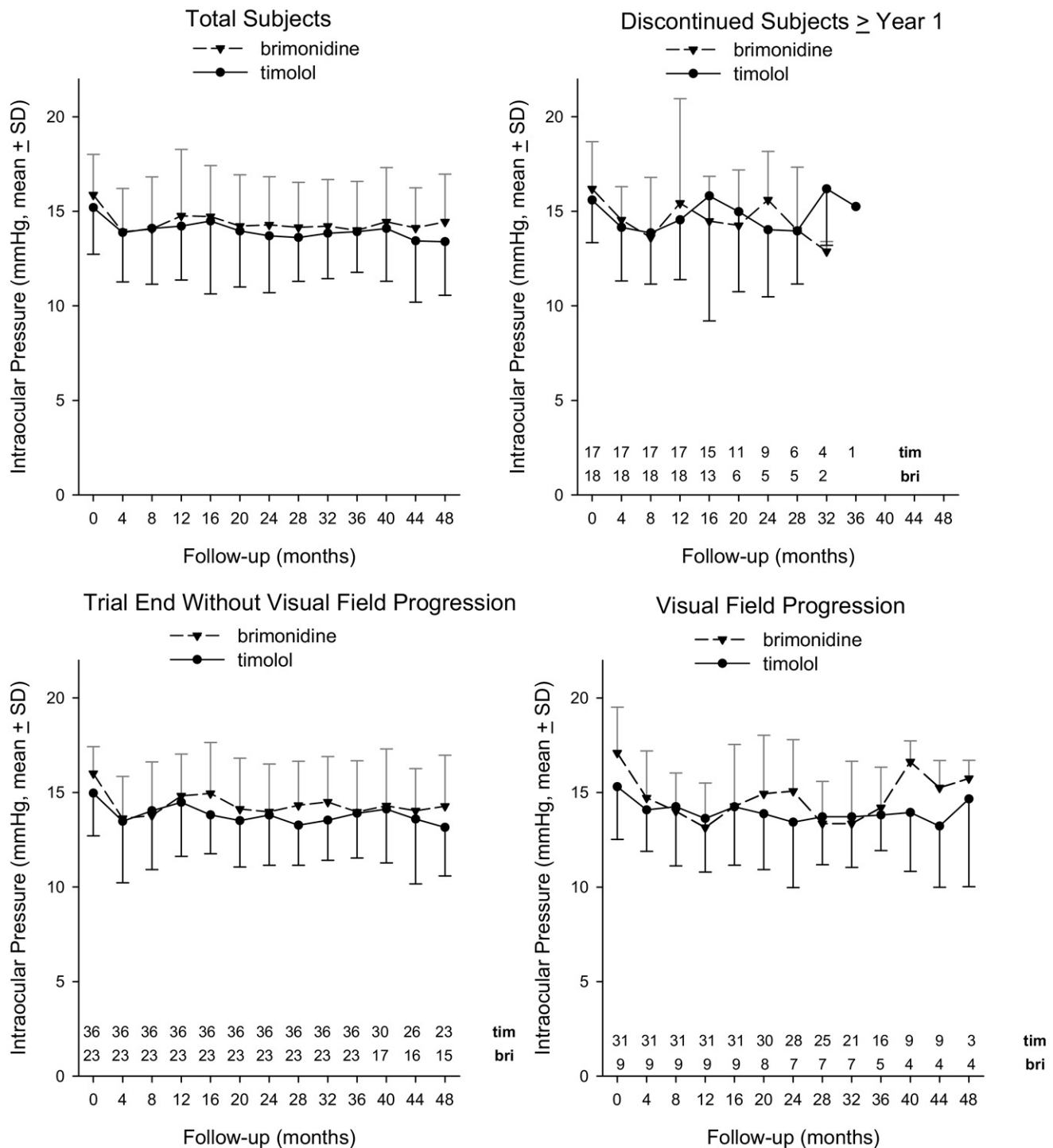
FIGURE 3. Distribution of intraocular pressure at baseline and follow-up visits for timolol and brimonidine treatment groups of the Low-pressure Glaucoma Treatment Study. Intraocular pressure data is illustrated for all subjects (top left), discontinued subjects ≥ year 1 (top right), trial end without visual field progression (bottom left) and visual field progression (bottom right). Up error bars (standard deviation) for brimonidine treatment, down error bars for timolol treatment. Data below each figure represent the number of study patients at the follow-up months.

negative slopes) also had significant positive slopes at other field locations.

Baseline characteristics of the 9 brimonidine and the 31 timolol patients manifesting visual field progression by point-wise linear regression were not significantly different with respect to age (66.0 ± 9.1 vs 65.7 ± 10.1 years), visual field mean deviation (−5.19 ± 3.90 vs −4.69 ± 5.02 dB), visual field pattern standard deviation (5.33 ± 2.23 vs 6.05 ± 2.52 dB), and diurnal IOP mean (16.9 ± 2.4 vs 15.4 ± 2.5) and standard deviation (1.5 ± 0.6 vs 1.5 ± 0.6). Baseline Snellen

TABLE 3. Intraocular Pressure Differences Between and Within Study Groups in the Low-pressure Glaucoma Treatment Study

	Timolol				Brimonidine				
	Num	Mean (SD)	95% CI	P^a	Num	Mean (SD)	95% CI	P^a	P^b
Dropout mo 16[c]	46	13.6 (2.6)	12.9–14.3		14	13.6 (2.2)	12.2–15.1		.86
vs >mo 16[d]	53	14.4 (1.9)	13.6–14.7	.23	65	14.2 (2.5)	13.6–14.9	.17	
vs study end[e]	43	14.2 (1.9)	13.6–14.8	.22	48	14.0 (2.6)	13.2–14.7	.21	

CI = confidence interval; mo = month; SD = standard deviation.
[a]Mann-Whitney U Test: *P* within groups.
[b]Mann-Whitney U Test: *P* between groups.
[c]Subjects dropping out before or at study month 16.
[d]Subjects dropping out before or at month 16; comparison to subjects in the study after month 16.
[e]Subjects dropping out before or at month 16; comparison to subjects reaching study end (month 36 or after) without visual field progression.

decimal fraction acuity in the 9 brimonidine progressing patients (0.92 ± 0.21) was statistically unchanged at the time of progression (0.89 ± 0.21), while the 31 timolol progressing patients had decreased Snellen decimal acuity (baseline 0.92 ± 0.21 vs 0.82 ± 0.19, *P* = .008) and decreased heart rate (baseline 70.1 ± 10.0 vs 66.0 ± 11.1, *P* = .016). Baseline refraction spherical equivalent was not significantly changed at the time of progression in either treatment group. Comparison of the linear regression slopes of the Snellen decimal fraction over time between brimonidine and timolol groups did not show a statistical difference for progressing patients (−0.001 ± 0.004 vs −0.002 ± 0.005), patients reaching study end (−0.001 ± 0.003 vs −0.002 ± 0.003), and patients not reaching the year-1 visit (0.009 ± 0.021 vs 0.018 ± 0.026). The linear regression slope for the brimonidine discontinued patients (−0.001 ± 0.004) was statistically negative (*P* = .051) compared to the timolol discontinued patients (0.003 ± 0.005).

The decrease in IOP was not significantly different in patients assigned to brimonidine or timolol (Figure 3). The distribution of IOP between the 2 groups during the study was similar at all time points for the total groups, discontinued patients, patients reaching study end without visual field progression, and the eyes manifesting visual field progression. The percent reduction of IOP and the number of patients with ≥20% IOP reduction during the study was not significantly different in the 2 treatment groups. IOP reduction ≥20% at the time of visual field progression by Progressor analysis was not significantly different (*P* = 1.000, Fisher 2-tailed test) between the timolol-treated (12/31, 39%) and the brimonidine-treated patients (4/9, 44%). Patients reaching study end without visual field progression (months 36–48) were also not significantly different (*P* = .403) regarding IOP reductions ≥20% (timolol 9/23, 39% and brimonidine 10/36, 28%).

Analyses were performed to determine whether there was a differential IOP between or within study groups (Table 3). There were no statistically significant differ-

ences in IOP between the treatment groups for subjects dropping out before month 16. Within treatment groups, there were no statistically significant IOP differences for subjects dropping out before month 16 compared to subjects in the study after month 16 or to subjects reaching study end (month 36 or after) without visual field progression.

Secondary visual field outcome measures were consistent with the primary outcome measure (see Table 2). Visual field progression by GCPM analysis was statistically less (log-rank 22.0, *P* = .001) in patients assigned to brimonidine (n = 8, 9 ± 4%) than those assigned to timolol (n = 35, 42 ± 7%). Evaluation by the 3-omitting method for pointwise linear regression showed the highest specificity of field progression that was also significantly less (log-rank 9.5, *P* = .002) in patients assigned to brimonidine (n = 5, 9 ± 4%) than to timolol (n = 21, 27 ± 6%).

Five patients assigned to brimonidine and 18 to timolol were detected as progressing by all 3 methods (Figure 4). Kappa (κ) ± SE analyses[23] were performed to measure patient agreement between the different methods to detect visual field progression and nonprogression. Agreement was substantial (defined as 0.61 < κ < 0.80) between Progressor pointwise linear regression and GCPM (0.625 ± 0.074) or Progressor pointwise linear regression and 3-omitting (0.719 ± 0.068), and moderate (defined as 0.41 < κ < 0.60) between GCPM and 3-omitting (0.554 ± 0.079). The overall agreement among the 3 methods was 0.628 ± 0.051.

DISCUSSION

LOW-PRESSURE GLAUCOMA PATIENTS RANDOMIZED TO monotherapy with brimonidine were statistically less likely to have progressive visual field loss than those patients randomized to monotherapy with timolol, despite known similar IOP lowering.[13,14,16,24] Determination of field progression by pointwise linear regression required the same 3
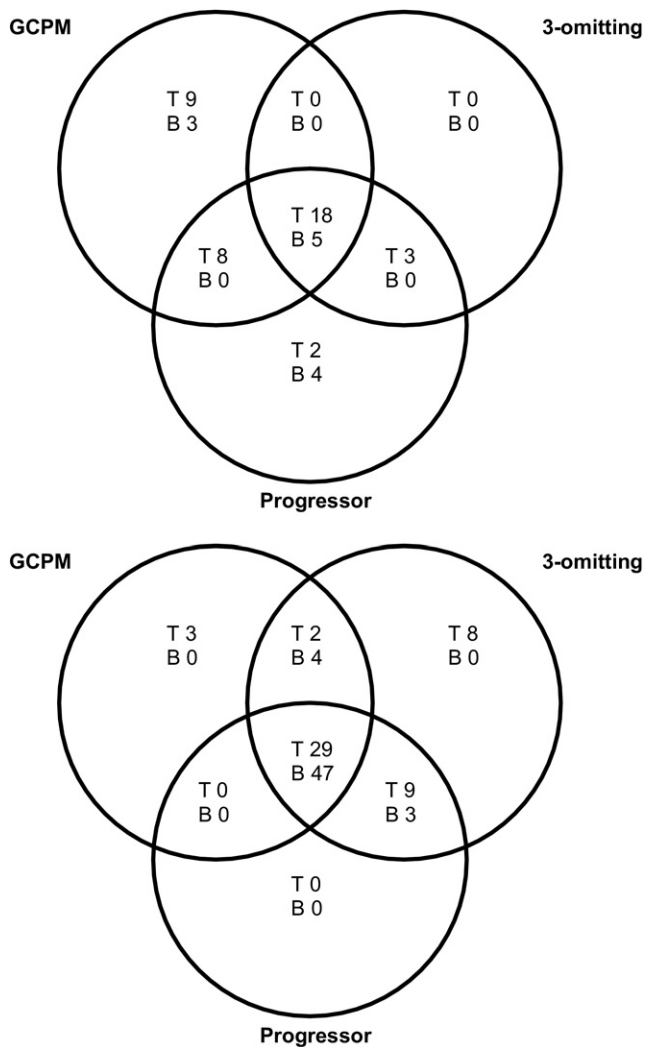
FIGURE 4. Venn diagrams illustrating agreement among visual field analysis methods for the Low-pressure Glaucoma Treatment Study. (Top) Patients judged to have visual field progression. (Bottom) Patients judged not to have visual field progression. GCPM = Humphrey glaucoma change probability maps using pattern deviation. 3-omitting = method for pointwise linear regression. Progressor = pointwise linear regression.

or more individual test locations to be progressing on 3 consecutive examinations over an 8-month interval.[25] Therefore, the first detection of field progression could only occur at the month-16 study visit. These stringent criteria[6,18] and linear regression analysis[17,26] were used to reduce the occurrence of false-positive determinations. There was good agreement between results of the primary pointwise linear regression and secondary (GCPM and 3-omitting for pointwise linear regression) visual field outcome measures.

The 4-year rate of visual field progression for the timolol-treated patients in our study (see Table 2) was 43.7% (31/71) for the Progressor analysis. This rate is similar to the reported 36% to 50% 3- to 5-year rates for visual field progression in low-pressure glaucoma.[3,17,27,28] The intent-to-treat analysis of the Collaborative Normal-Tension Glaucoma Study (CNTGS), which used a different method to define progression than the current study, reported similar 3-year rates of visual field progression in the IOP-lowered (22/66, 33%) and the untreated (31/79, 39%) arms.[11] Significant differences favoring treatment were detected in CNTGS only after additional analyses censored for cataract and the baseline visual field was defined as after the IOP reduction goal was achieved.[10] Both of the medications used in the current study were either excluded by intent (timolol) or not available (brimonidine) in CNTGS. The timolol 3-year progression rate in the current study by Progressor analysis was 31.0% (22/71).

Given that the IOP reduction was similar between groups (see Figure 3), the lower rate of visual field progression in brimonidine-treated patients could result from either an unknown IOP effect or an IOP-independent process. While brimonidine and timolol produced similar reduction of measured IOP in this study, it is possible that brimonidine was more effective than timolol in lowering diurnal, peak, mean, or nocturnal IOP. These IOP parameters were not measured in the current study. A related explanation could be different mechanisms of action. The reduction of aqueous humor production by timolol is minimal at night,[29] while brimonidine has been reported to both reduce aqueous humor production and increase uveoscleral outflow.[30]

If the lower progression rate in patients randomized to brimonidine is attributable to IOP-independent effects, then either brimonidine was relatively protective, timolol was relatively harmful, or both. Lower diastolic[31–34] and systolic[35] ocular perfusion pressures have been identified as risk factors for glaucoma progression. The difference in visual field progression in the current study could result from timolol producing greater systemic hypotension and bradycardia than brimonidine[36] with induced nocturnal arterial hypotension[37] and alteration of ocular perfusion pressures. Countering this explanation are the findings of Quaranta and associates,[38] demonstrating a greater reduction of mean 24-hour systolic blood pressure, diastolic blood pressure, and calculated diastolic ocular perfusion pressure with brimonidine than timolol, suggesting that any alteration in perfusion pressure caused by these 2 agents would, if anything, be worse in the brimonidine group. While this supports a protective rather than a vasoactive mechanism of action for the reduced visual field progression in the brimonidine-treated patients, it remains possible that another, not yet described timolol- or brimonidine-related vascular (or other) phenomenon could account for the results of the present study.

Neuroprotection, the therapeutic paradigm designed to slow or prevent the death of neurons to maintain physiological function, has been a goal of neuroscientists to treat

central nervous system disease. With the exception of memantine for Alzheimer disease[39] and riluzole for amyotrophic lateral sclerosis,[40] clinical trials in neuroprotection have failed to demonstrate improved outcomes. The multiple stroke clinical trial failures highlight potential pitfalls that can occur when translating results from animal models into heterogeneous patient populations, as well as the brief window of time when treatment can be effective.[41,42]

Open-angle glaucoma, a slowly progressive degeneration of RGCs, has a number of characteristics that lend themselves to the investigation of neuroprotection therapies.[43] While the current management of glaucoma continues to be focused on lowering IOP, this treatment is not always successful in halting disease progression, suggesting that factors other than IOP contribute to the disease. In vitro studies of RGCs and animal models of optic nerve injury and elevated IOP have elucidated mechanisms for RGC death[44] by apoptosis.[45] Finally, established clinical methods are available for detection of glaucomatous optic nerve and visual field progression to assess the effect of neuroprotective intervention. However, 2 large multicenter clinical trials studying the neuroprotective effect of the N-methyl-D-aspartate (NMDA) receptor antagonist memantine in glaucoma failed to show efficacy at their primary endpoints.[46]

The alpha2-adrenergic agonist dexmedetomidine was shown in 1993 to be neuroprotective in animal models of focal cerebral ischemia.[47] Subsequent animal[48,49] and human[49,50] studies demonstrated the presence of alpha2-adrenergic receptors in the retina. Systemic administration of brimonidine protected RGCs following partial crush injury to the rat optic nerve[51] and in ocular hypertensive rat models.[52,53] Potential mechanisms for these neuroprotective effects include upregulation of brain-derived neurotrophic factor in RGCs[54] and the retina,[55] activation of cell-survival signaling pathways and anti-apoptotic genes,[48] and modulation of N-methyl-D-aspartate receptor function.[56]

Brimonidine activates the alpha2-adrenergic agonist receptor in cell culture at a minimum concentration of 2 nM (0.88 ng/mL).[57,58] Topical administration of brimonidine produces drug concentrations in the vitreous (1.4-1836 nM) in humans.[59] While receptor expression in cell culture can differ from that in vivo, vitreal brimonidine levels provide a drug delivery route to the RGC sufficient to bind and activate the alpha2-adrenergic receptor. In this way, brimonidine theoretically could function to maintain the health of the optic nerve independent of its ability to reduce IOP, a use that is currently not a component of the FDA-approved labeling for any alpha2-adrenergic agonist.

Our study protocol planned for more discontinuations in the brimonidine-treated compared to timolol-treated patients and randomized treatment in blocks of 7, 4 to brimonidine and 3 to timolol. Ocular adverse events in our patients receiving brimonidine 0.2% twice daily were similar to other reports.[13,14,16,24] While ocular allergy may have revealed the brimonidine treatment assignment, our study design relied upon masking of study medication and the analysis of the visual fields. Data from dropouts were examined and statistically evaluated at the last study visit. However, these patients were not followed in the study protocol since subsequent therapy often did not meet the protocol's monotherapy design, resulted in treatment with an alternate study medication, or included treatment with initial exclusion criteria, such as surgical intervention. While baseline characteristics were similar between dropouts and patients completing the year-1 and later visits within the brimonidine- and the timolol-assigned patient groups, the failure to obtain information from the dropouts limits interpretation of the results, and the unequal dropout between the groups could introduce bias if patients who dropped out were also more likely to have shown progression.

In summary, in this randomized clinical trial, twice-daily treatment with topical brimonidine tartrate 0.2% preserves visual field better than treatment with topical timolol maleate 0.5% in a subset of open-angle glaucoma patients with statistically normal IOP. Given the similar IOP-lowering efficacy of the 2 compounds, this finding is consistent with a non-IOP-related mechanism of action favoring brimonidine-treated patients. The effectiveness of brimonidine in delaying or preventing visual field progression has to be judged in context of brimonidine's adverse event profile, primarily localized external ocular allergy. Validation of a neuroprotective mechanism of action requires additional basic science and clinical research to confirm the present results prior to altering current clinical patient care paradigms.

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