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Fourteen-Year Outcome of Angle-Closure Prevention with Laser Iridotomy in the Zhongshan Angle-Closure Prevention Study

Extended Follow-up of a Randomized Controlled Trial

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Purpose: This study aimed to evaluate the efficacy of laser peripheral iridotomy (LPI) prophylaxis for patients with primary angle-closure suspect (PACS) after 14 years and to identify risk factors for the conversion from PACS to primary angle closure (PAC).

Design: Extended follow-up of the Zhongshan Angle-Closure Prevention Study.

Participants: Eight hundred eighty-nine Chinese patients 50 to 70 years of age with bilateral PACS.

Methods: Each patient received LPI in 1 randomly selected eye, with the fellow untreated eye serving as a control. Because the risk of glaucoma was low and acute angle closure (AAC) occurred only rarely, the follow-up was extended to 14 years despite substantial benefits of LPI reported after the 6-year visit.

Main Outcome Measures: Incidence of PAC, a composite end point including peripheral anterior synechiae, intraocular pressure (IOP) of $>$ 24 mmHg, or AAC.

Results: During the 14 years, 390 LPI-treated eyes and 388 control eyes were lost to follow-up. A total of 33 LPI-treated eyes and 105 control eyes reached primary end points ($P < 0.01$). Within them, 1 LPI-treated eye and 5 control eyes progressed to AAC. Primary angle-closure glaucoma was found in 2 LPI-treated eyes and 4 control eyes. The hazard ratio for progression to PAC was 0.31 (95% confidence interval, 0.21−0.46) in LPI-treated eyes compared with control eyes. At the 14-year visit, LPI-treated eyes showed more severe nuclear cataract, higher IOP, and larger angle width and limbal anterior chamber depth (LACD) than control eyes. Higher IOP, shallower LACD, and greater central anterior chamber depth (CACD) were associated with an increased risk of end points developing in control eyes. In the treated group, eyes with higher IOP, shallower LACD, or less IOP elevation after the darkroom prone provocative test (DRPPT) were more likely to demonstrate PAC after LPI.

Concluions: Despite a two-third decrease in PAC occurrence after LPI, the cumulative risk of progression was relatively low in the community-based PACS population over 14 years. Apart from IOP, IOP elevation after DRPPT, CACD, and LACD, more risk factors are needed to achieve precise prediction of PAC occurrence and to guide clinical practice.

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Primary angle-closure glaucoma (PACG) is one of the most significant irreversible blinding eye diseases worldwide.[1] It is estimated that $>$ 32 million patients will have PACG by 2040, about three quarters of whom are Asian. In China, approximately 28.2 million patients with suspicion of primary angle closure (PAC) and 9.1 million patients with PAC may go on to demonstrate PACG.[2] Prophylactic laser peripheral iridotomy (LPI) traditionally has been recommended for patients with primary angle-closure suspect (PACS) to prevent angle closure. However, considering the large-scale population at risk for PACG, mass laser intervention is an expensive proposition that requires strong evidence to endorse this as a massive prophylactic strategy.[3,4]

The Zhongshan Angle-Closure Prevention (ZAP) Study is a randomized controlled trial that enrolled 889 participants with bilateral PACS from Guangzhou, China. With 1 eye treated by LPI and the other remaining untreated as a control, the ZAP Study showed that LPI achieved a 50% reduction in the 6-year risk of PAC progression in PACS.[5]

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More recently, the Singapore Asymptomatic Narrow Angles Laser Iridotomy Study (ANA-LIS) further confirmed the aforementioned findings in the context of Singaporean hospitals.[6]

Although identifying risk factors associated with the increased risk of PAC occurrence is an objective of both of these studies,[7–9] it is underpowered to explore prophylactic effects within different groups and to develop prediction models because of the low event rates observed in the 6-year study. Therefore, we extended the study and completed a 14-year follow-up period for the ZAP Study to report (1) the level of LPI that reduces the risk of end point events among patients with PACS in the long term and (2) the natural course of PACS over time, as well as risk factors related to PACS progression.

Methods

Design, Participants, and Procedures of the ZAP Study

The ZAP Study was a single-center randomized controlled trial, and its protocol has been published previously.[5,9] Briefly, 11 991 community residents 50 to 70 years of age were screened for bilateral PACS (invisible pigmented trabecular meshwork with ≥ 6 clock hours under static gonioscopy) in Guangzhou, China. Exclusion criteria included peripheral anterior synechiae (PAS), intraocular pressure (IOP) of > 21 mmHg, corneal opacity, visual impairment (< 20/40), history of intraocular surgeries, penetrating ocular trauma, or acute angle closure (AAC) characterized by anterior segment abnormalities including iris whirling, glaukomflecken, or excessive trabecular pigment deposition. In addition, patients with IOP elevation of > 15 mmHg after the darkroom prone provocative test (DRPPT) were deemed to be at risk of AAC and also were excluded. For each eligible participant, one eye was selected randomly to be treated with LPI, and the other eye was kept untreated as a control. The LPI was conducted by a trained ophthalmologist using the Abraham lens (Ocular Instruments). Yttrium–aluminum–garnet laser (Visulas YAG III; Carl Zeiss Meditec) with a starting energy setting of 1.5 mJ and a minimum diameter of 200-μm spot was used, targeting the crypt or the thinnest of iris, which could be obscured by the upper lid during eye opening. Except for baseline examinations, treated and untreated eyes were examined at 2 weeks and then at 0.5, 1.5, 3, 4.5, and 6 years after the LPI intervention in the 6-year ZAP Study.

Examinations and Outcomes in the 14-Year Extended Study

After the 6-year visit, all participants were informed that the risk of vision impairment resulting from AAC or PACG was extremely low and that it was not necessary to receive prophylactic LPI in the control eye based on existing evidence. Until the 14-year visit, all living participants of the ZAP Study were invited to this extended follow-up with the same examination protocols. The extended study was approved by the Zhongshan Ophthalmic Center Ethical Review Committee and was performed in accordance with the tenets of the Declaration of Helsinki. All participants signed informed consent forms before enrollment and each follow-up.

Using a Goldmann-type single-mirror gonioscope (Ocular Instruments), static gonioscopy was performed in a standard dark environment (< 1 lux) with a narrow 1-mm beam. The angle widths between the surface tangent of the trabecular meshwork and the peripheral one-third volume of the iris were assessed using the Shaffer grading system in each quadrant. The angle widths were recorded for 5 classification points (Shaffer grading 0–4 representing 0°, 10°, 20°, 30°, and 40° angle widths). If the forward bulging of the iris made observation of the angle difficult, it was allowed to tilt the gonioscope slightly (< 10°) to determine whether it was open. If trabecular meshwork was not visible, the presence of PAS was determined by dynamic examination with a 4-mirror gonioscope (Ocular Instruments). If iridotrabecular contact could be restored by compression, then the patient was considered to have PACS and was eligible for enrollment. Gonioscopy was performed by a glaucoma specialist (W.W.) with standardized training and > 10 years of experience (weighting κ values > 0.80 with examiners in previous follow-ups).

Presenting visual acuity was measured using the Early Treatment Diabetic Retinopathy Study logarithm of the minimum angle of resolution E-chart (Precision Vision). The IOP was assessed first using Goldmann applanation tonometry by a trained nurse who was unaware of the LPI treatment. Three IOP measurements were recorded at each visit, and the average value was calculated. During the DRPPT, a Tono-Pen applanation tonometer (Tono-Pen XL; Medtronic) was used to measure IOP before and after 15 minutes of lying in the darkroom (< 1 lux) with the foreface down. Ocular biometric parameters, including central anterior chamber depth (CACD) and lens thickness, were measured by ultrasound A-scan biometry (CineScan A/B; Quantel Medical) after topical anesthesia. Both eyes underwent 24-2 Fast visual field tests using the Humphrey Field Analyzer HFA-II (Carl Zeiss Meditec). Repeated tests were required if false-positive or negative-error rates were larger than 33%. The limbal anterior chamber depth (LACD) was assessed using a modified van Herick grading method with a slit lamp (BQ-900; Haag-Streit). The depth of the temporal anterior chamber at the corneoscleral junction was expressed as a percentage of the adjacent corneal thickness. For examination of the lens, optic disc, macula, and peripheral retina, 0.5% tropicamide and 5% phenylephrine eye drops were used to dilate the pupil. The Lens Opacity Classification System III was used to grade cataracts with reference to standard photographs. Lens color and opalescence, cortical cataracts, and posterior subcapsular cataracts were assessed using 6, 5, and 5 retroillumination images, respectively.

The primary outcome was the risk of PAC occurrence, consisting of the following 3 study end points: (1) IOP of > 24 mmHg confirmed by a recheck on another day within 1 week, (2) PAS of 1 clock hour or more in either quadrant, or (3) AAC. The secondary outcomes were presenting visual acuity, IOP, total angle width on gonioscopy, LACD, CACD, lens thickness, and cataract grading scores. Due to its rare incidence, PACG was diagnosed as a secondary outcome based on glaucomatous optic neuropathy together with visual field defects in PAC eyes.

Statistical Analyses

The analyses of primary outcomes were based on the intention-to-treat principle, which included randomly assigned patients, and the per-protocol principle was adopted for the sensitivity analysis. Baseline characteristics were compared between different groups using within-subject analyses of variance and chi-square tests. The efficacy of LPI to prevent PAC progression was assessed using the McNemar test. Kaplan–Meier survival curves were used to show event rates, and log-rank tests were used to test the equilibrium of the survival curves. To account for both time and events between LPI-treated eyes and control eyes, univariable and multivariable Cox proportional hazards regression models were built to evaluate the association of LPI intervention and PAC occurrence, which reported hazard ratios (HRs) and 95% confidence intervals (CIs) after adjusting for baseline covariates. Data for eyes that underwent

cataract surgeries were removed at the last follow-up visit before cataract surgery. In sensitivity analyses, competing risk Cox regression was performed with cataract surgery treated as a competing risk. Logistic regression models also were built, which included only eyes that reached the primary end points or were censored at the 14-year visit. Based on significant risk factors, univariable and multivariable logistic models were built to predict the 14-year occurrence of PAC in control eyes and LPI-treated eyes, respectively. Predictive efficacy was assessed using the area under the receiver operating characteristic curve. For each risk factor, the optimal cutoff value was determined by the Youden index. Sensitivity, specificity, and categorical odds ratios beyond the cutoff value were reported. Secondary outcomes were compared between LPI-treated eyes and control eyes using paired *t* tests. All statistical analyses were performed using Stata version 15.1 software (StataCorp LLC). The significance level of the 2-sided test was set at 0.05. The trial was registered on the ISRCTN registration platform (identifier, ISRCTN45213099).

Results

From 2008 through 2022, a total of 889 eligible participants received LPI intervention in a randomly selected eye and participated in the follow-up. Figure 1 illustrates the flow process of the study. The mean age of the enrolled patients was 59.3 ± 5.0 years, and 737 participants (83%) were women. The comparison of baseline characteristics was reported in previous studies, which were balanced between LPI-treated eyes and control eyes.[5,9] This was the 14-year extended follow-up of the ZAP Study, which was completed in 499 eyes (56.13%) and 501 eyes (56.36%) of the 889 eyes in the treatment and control groups, respectively. The mean duration of follow-up was 8.70 ± 4.91 years in the LPI-treated eyes and 8.69 ± 4.92 years in the control eyes. Patients who declined follow-up or were lost to follow-up were significantly older and had higher IOP at baseline. A total of 70 LPI-treated eyes and 54 control eyes received cataract surgery before the 14-year visit or end points were reached. Except for being older, eyes receiving cataract surgery also had lower IOP and more severe nuclear, cortical, and posterior subcapsular cataract than the remaining eyes at baseline (Table S1, available at www.aaojournal.org).

Until the 14-year visit, 33 LPI-treated eyes (4.27 eyes per 1000 eye-years) and 105 control eyes (13.59 eyes per 1000 eye-years) reached the primary end point (Tables 1 and 2). After adjusting for the intereye correlations, the primary outcome between the treated and untreated eyes remained significant using McNemar pairwise tests in the intention-to-treat analysis ($P < 0.01$). The per-protocol analysis was performed by excluding participants who were lost to follow-up, who underwent cataract surgery, and who underwent LPI in the control eye, of which the findings remained statistically significant (Table 1). We also analyzed the primary outcome using a Cox model, and the risk of reaching the end point was reduced by 69.9% in the LPI-treated eyes (HR, 0.31; 95% CI, 0.21−0.46; Fig 2). Accordingly, the number needed to treat (NNT) was 12.35 (95% CI, 9.42−17.67) to prevent 1 PAC occurrence over 14 years.

The benefit of treatment was achieved mainly by reducing the development of PAS (LPI, 3.62 per 1000 eye-years vs. control, 12.68 per 1000 eye-years; NNT, 12.70; 95% CI, 9.71−18.05; $P < 0.01$; Table 2). In LPI-treated eyes, the proportion of PAS of 2 clock hours or more was slightly lower than that in control eyes (4/28 [14.3%] vs. 28/98 [28.6%]; $P = 0.33$). Compared with baseline measurements, presenting visual acuity (PVA), total angle width score, and LACD were decreased slightly in PAS eyes ($P < 0.01$). By contrast, IOP was increased moderately after PAS formation (15.75 ± 2.88 mmHg vs. 16.42 ± 3.20 mmHg; $P = 0.02$), with IOP of 21 mmHg or more found in only 11 PAS eyes (8.73%; Table S2, available at www.aaojournal.org). Intraocular pressure elevation of 24 mmHg or more was uncommon in both groups (LPI, 0.52 per 1000 eye-years vs. control, 0.78 per 1000 eye-years; NNT = 444.50; $P = 0.53$). In the 10 eyes reaching the IOP end point, PAS of 1 clock hour or more was found in 3 control eyes, and 1 eye showed PAS of 2 clock hours or more. Only 1 LPI-treated eye and 5 control eyes showed AAC (LPI, 0.13 per 1000 eye-years vs. control, 0.65 per 1000 eye-years; NNT, 222.25; $P = 0.10$), with PAS of 2 clock hours or more found in 1 control eye. Primary angle-closure glaucoma was diagnosed in 2 LPI-treated eyes and 4 control eyes, with bilateral PACG found in 1 patient (Table S3, available at www.aaojournal.org). At the 14-year visit, LPI-treated eyes showed larger total angle width (7.63 ± 3.02 vs. 2.04 ± 2.60; $P < 0.01$) and LACD (29.97 ± 11.06% vs. 14.91 ± 7.63%; $P < 0.01$) than the control eyes. Statistical differences also were found in IOP and nucleus cataract degrees, both of which were slightly higher in LPI-treated eyes ($P < 0.01$). No statistical difference was found in other secondary outcomes at the 14-year visit (Table S4, available at www.aaojournal.org).

In univariable models, the increased risks of PAC occurrence were found in eyes with higher IOP, narrower total angle width, and shallower LACD and CACD at baseline. In multivariable models adjusting for all covariates (mean variance inflation factor, 1.12), IOP (per 1 mmHg higher: HR, 1.12; 95% CI, 1.05−1.18), LACD (per 10% higher: HR, 0.64; 95% CI, 0.49−0.82), and CACD (per 1 mm higher: HR, 0.89; 95% CI, 0.82−0.98) were associated significantly with the increased risk of PAC occurrence over 14 years (Table 3). In subgroup analyses, associations between IOP and LACD with PAC occurrence remained statistically significant in both control eyes and LPI-treated eyes, respectively (Table 4). However, CACD was associated significantly with PAC occurrence only in control eyes. In treated eyes, less IOP elevation after DRPPT was associated significantly with the increased risk of PAC (per 1 mmHg higher: HR, 0.87; 95% CI, 0.77−0.97), which was different from its counterpart in control eyes ($P < 0.05$ for interaction with LPI). These findings also were supported by competing risk models (Table S5, available at www.aaojournal.org) and logistic regression models (Tables S6 and S7, available at www.aaojournal.org). Determined by the Youden index, cutoff values of IOP, LACD, CACD, and IOP changes after DRPPT allowed preliminary stratification for eyes with 2- to 3-times-higher PAC risks (Table 5). To predict PAC occurrence over the 14 years in control eyes, multivariable logistic models consisting of IOP, LACD, and CACD provided better performance than univariable models (area under the receiver operating characteristic curve, 0.70; 95% CI, 0.64−0.76). Intraocular pressure, LACD, IOP elevation after DRPPT, and their combination showed similar performance in LPI-treated eyes (area under the receiver operating characteristic curve, 0.62−0.71).

Discussion

Principal Findings

To the best of our knowledge, the ZAP Study remains the largest single-center clinical trial to provide evidence for better preventive treatment decisions in patients at risk of PAC. Eyes treated with LPI showed a 69% reduced risk of PAC occurrence, with much of this difference owing to a nearly threefold higher risk of PAS in the control eyes. Even after up to 14 years of extended follow-up, the rate of events

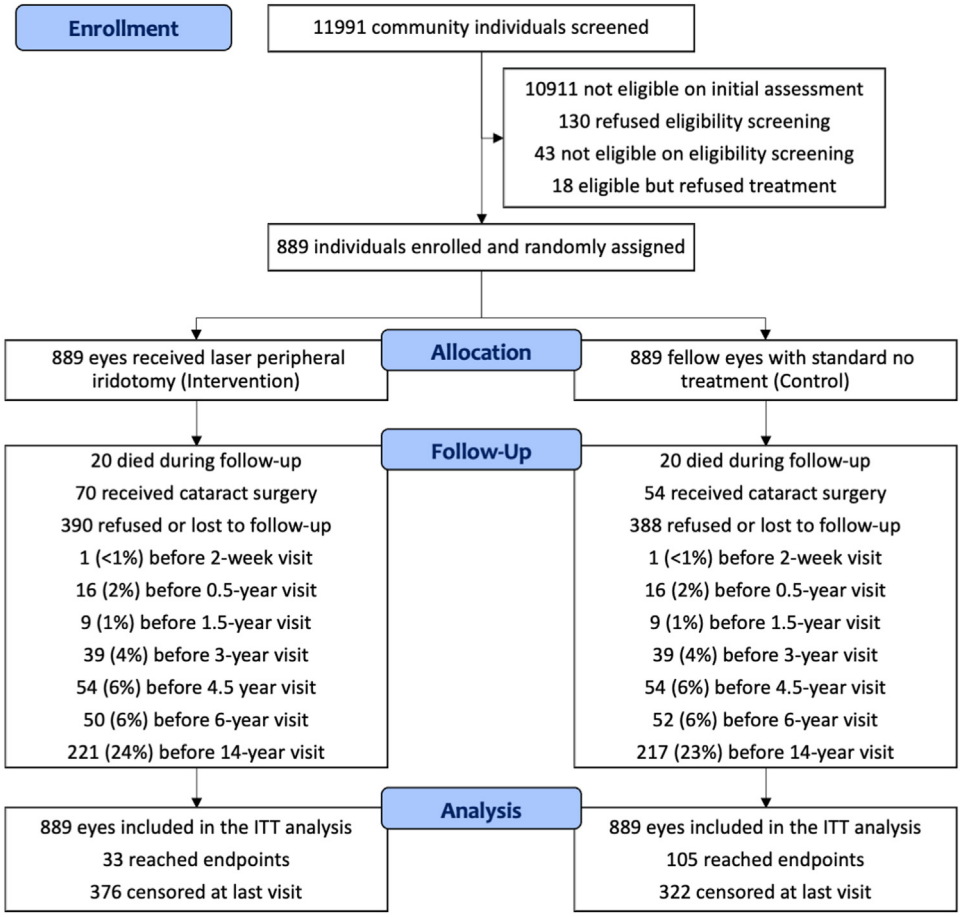

Figure 1. Flow diagram showing study profile. ITT = intention-to-treat.

that reached the end point remained quite low. In the untreated eyes, increased IOP, decreased LACD, and CACD at baseline were associated significantly with the risk of reaching the end point. In the treated eyes, a lower level of IOP elevation after DRPPT at baseline was identified as an additional risk factor for primary end points.

Table 1. Pairwise Analysis of the Study End Point at the 14-Year Visit

Variable	Laser Peripheral Iridotomy		
	No End Point	*End Point*	*Total*
Intention-to-treat analysis			
Control			
No end point	771 (86.73)	13 (1.46)	784 (88.19)
End point	85 (9.56)	20 (2.25)	105 (11.81)
Total	856 (96.29)	33 (3.71)	889 (100.00)
Per-protocol analysis			
Control			
No end point	289 (74.87)	5 (1.30)	294 (76.17)
End point	72 (18.65)	20 (5.18)	92 (23.83)
Total	361 (93.52)	25 (6.48)	386 (100.00)

Data are presented as n (%). Both $P < 0.01$ with the McNemar test.

Natural History of PACS

Few longitudinal studies have described the natural history of PACS eyes. In an Indian population, Thomas et al[10] reported a 5-year conversion rate from PACS to PAC of 22%; however, the credibility of the data has been questioned because this incidence was derived from only 82 patients with PACS. Ye et al[11] followed up 485 patients with PACS for 6 years and found that 20 patients (4.1%) progressed to PACG. In an Inuit population, Wilensky et al[12] followed up 129 patients with PACS and found that 25 patients (19.4%) progressed to PAC during a mean of 2.7 years of follow-up. In the recent Singapore Epidemiology of Eye Diseases Study, which included 222 patients with PACS over 6 years of follow-up, 9.38% progressed to PAC or PACG.[13] In the population-based Handan Eye Study, which included 526 patients with PACS over 5 years of follow-up, 32 patients progressed (31 patients with PAC and 1 patient with PACG) at a rate of 6.08%.[14] The only study conducted for > 10 years reported a 35% progression rate of PACS in Inuit patients.[15] It is worth noting that the previously mentioned studies used a wide variety of definitions of angle closure. In the ANALIS study, 9.4% of patients with PACS (21.84 per 1000 eye-years) progressed over 5 years of follow-up, compared

Table 2. Primary End Points at the 14-Year Visit by Intention-to-Treat Analysis

	Laser Peripheral Iridotomy (n = 889)	Control (n = 889)	P Value
Reach primary end point	33 (4.27 per 1000 eye-years)	105 (13.59 per 1000 eye-years)	< 0.01
Before 6 yrs	19	36	
7–14 yrs	14	69	
IOP > 24 mmHg	4 (0.52 per 1000 eye-years)	6 (0.78 per 1000 eye-years)	0.53
Before 6 yrs	3	5*	
7–14 yrs	1	1	
PAS ≥ 1 clock hour	28 (3.62 per 1000 eye-years)	98 (12.68 per 1000 eye-years)	< 0.01
Before 6 yrs	15	30	
7–14 yrs	13	68	
Acute attack	1 (0.13 per 1000 eye-years)	5 (0.65 per 1000 eye-years)	0.10
Before 6 yrs	1	5*	
7–14 yrs	0	0	

IOP = intraocular pressure; PAS = peripheral anterior synechiae.
All values are the number of events unless stated otherwise. *P* values were estimated by log-rank tests for equality of survival function.
*Four control eyes reached both the PAS end point and IOP or acute attack end point at the same visit.

with the 14-year cumulative risk of in this study (11.81%), which may be related to the hospital-based population and more lenient definitions of end points.[6] Notably, the vast majority (98/105) of the eyes that progressed to PAC showed evidence of mild PAS, a benign disorder, with about 2% to 6% of PAS eyes progressing to PACG annually.[16,17] In this study, IOP increases of > 21 mmHg were found in only 7 control eyes (7.14%) at PAS diagnosis. After laser or cataract surgery, most eyes with PAS that is diagnosed within the first 6 years could remain stable over the long term. Until the 14-year visit, only 4 control eyes demonstrated PACG and needed further antiglaucoma treatments.

Efficacy of Prophylactic LPI

Both paired tests and Cox models demonstrated that LPI reduced the incidence of PAC by approximately two thirds. The only direct comparable data were from the ANA-LIS study, which also focused on patients of Chinese ethnicity.[6] Within the 5-year follow-up for the ANA-LIS study, LPI was associated significantly with a 45% reduced risk of PAC progression in patients with PACS. The event rates for IOP elevation and AAC were extremely low and were not significantly different between LPI-treated eyes and control eyes in both studies, which suggests that the risk of acute episodes in patients with PACS

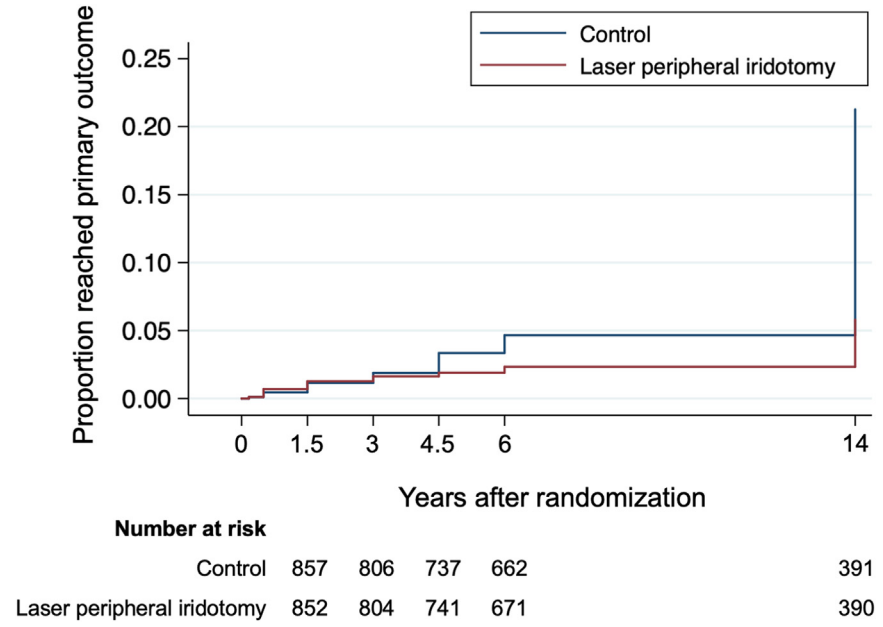

Figure 2. Kaplan–Meier failure estimation plot of the study end point. The hazard ratio for laser peripheral iridotomy was 0.31 (95% confidence interval, 0.21–0.46).

Table 3. Cox Regression Models of the Association between Baseline Factors and Primary End Points at the 14-Year Visit

	Eyes That Did Reach End Points (n = 138 [8%])	Eyes That Did Not Reach End Points (n = 1634 [92%])	Univariable Model		Multivariable Model	
			Hazard Ratio (95% Confidence Interval)	*P Value*	*Hazard Ratio (95% Confidence Interval)*	*P Value*
LPI (vs. control)	23.91%	52.33%	0.31 (0.21–0.46)	< 0.01	0.31 (0.21–0.45)	< 0.01
Age per 1 yr of age (yrs)	59.02 ± 5.07	59.35 ± 5.02	1.02 (0.99–1.06)	0.24	1.02 (0.98–1.06)	0.31
Female sex (vs. male)	85.51%	82.74%	1.17 (0.73–1.87)	0.52	0.92 (0.56–1.50)	0.73
Baseline IOP per 1 mmHg higher (mmHg)	15.86 ± 2.87	15.03 ± 2.82	1.12 (1.06–1.19)	< 0.01	1.12 (1.05–1.18)	< 0.01
Total angle width per 1 score higher (score)*	4.75 ± 2.61	5.39 ± 2.36	0.90 (0.84–0.97)	< 0.01	0.96 (0.89–1.03)	0.29
ACD						
Limbal per 10% higher (%)†	19.60 ± 8.71	22.37 ± 7.49	0.57 (0.45–0.72)	< 0.01	0.64 (0.49–0.82)	< 0.01
Central per 0.1 mm higher (mm)‡	2.50 ± 0.23	2.55 ± 0.22	0.87 (0.80–0.94)	< 0.01	0.89 (0.82–0.98)	0.02
Lens thickness per 1 mm higher (mm)‡	4.91 ± 0.31	4.87 ± 0.32	1.78 (1.00–3.16)	0.05	1.03 (0.54–1.96)	0.94
DRPPT per 1 mmHg higher (mmHg)	4.29 ± 2.97	4.25 ± 2.99	0.99 (0.93–1.04)	0.61	0.97 (0.92–1.03)	0.39

ACD = anterior chamber depth; DRPPT = darkroom prone provocative test; IOP = intraocular pressure; LPI = laser peripheral iridotomy
All values are mean ± standard deviation unless otherwise indicated. Multivariable Cox regression models include LPI, age, sex, baseline IOP, and variables of interest. Six eyes with unavailable A-scan results were excluded.
*Total angle width was calculated by the sum of Shaffer grading of all 4 quadrants (range, 0–16; a larger number indicates wider angle).
†Evaluated by modified van Herick grading.
‡Measured by ultrasound A-scan.

was substantially lower than initially expected before the LPI intervention. Despite the NNT dropping to 12.35 after the extended 14-year follow-up, prophylactic LPI should be recommended preferentially to those at the highest risk of angle closure because the annual incidence of PAC was low and AAC and PACG were relatively rare in the community-based population with PACS over the long-term. This study also proved the long-term safety of LPI intervention, with similar visual acuity found between LPI-treated eyes and control eyes. Despite higher degrees of nuclear cataract found in treated eyes, prophylactic LPI led to only 16 additional cataract surgeries in 889 patients with PACS (17.12 ‰) during the 14 years of the study. Considering that more than two thirds of cataract surgeries occurred 6 years after LPI, its effect on long-term cataract progression and relevant clinical significance should be ascertained in further studies. Similarly with 6-year findings, a slightly higher IOP was found in treated eyes at 14 years, which might be attributed to inflammation responses after LPI and dynamic changes of aqueous humor outflow.

Table 4. Multivariable-Adjusted Cox Models for the Association between Baseline Factors and Primary End Points at the 14-Year Visit in Control Eyes and Treated Eyes

	Control (n = 884)		Laser Peripheral Iridotomy (n = 888)	
	Hazard Ratio (95% CI)	*P Value*	*Hazard Ratio (95% CI)*	*P Value*
Age per 1 yr of age (yrs)	1.01 (0.97–1.06)	0.57	1.03 (0.96–1.11)	0.36
Female sex (vs. male)	0.95 (0.53–1.68)	0.85	0.86 (0.32–2.29)	0.76
Baseline IOP per 1 mmHg higher (mmHg)	1.11 (1.04–1.19)	< 0.01	1.14 (1.02–1.28)	0.03
Total angle width per 1 score higher (score)*	0.98 (0.90–1.06)	0.60	0.92 (0.79–1.06)	0.24
ACD				
Limbal per 10% higher (%)†	0.70 (0.52–0.93)	0.02	0.45 (0.27–0.76)	< 0.01
Central per 0.1 mm higher (mm)‡	0.88 (0.79–0.98)	0.02	0.94 (0.78–1.13)	0.50
Lens thickness per 1 mm higher (mm)‡	1.19 (0.56–2.54)	0.65	0.69 (0.21–2.29)	0.54
DRPPT per 1 mmHg higher (mmHg)§	1.01 (0.95–1.08)	0.69	0.87 (0.77–0.97)	0.02

ACD = anterior chamber depth; CI = confidence interval; DRPPT = darkroom prone provocative test; IOP = intraocular pressure.
Multivariable Cox regression models include age, sex, IOP, and variables of interest. Six eyes with unavailable A-scan results were excluded.
*Total angle width was calculated by the sum of Shaffer grading of all 4 quadrants (range, 0–16; a larger number indicates wider angle).
†Evaluated by modified van Herick grading.
‡Measured by ultrasoud A-scan.
§$P < 0.05$ for interaction with laser peripheral iridotomy treatment.

Table 5. Univariable and Multivariable Logistic Models to Predict Primary End Points in Control Eyes and Treated Eyes That Reached the Primary End Points or Were Censored at the 14-Year Visit

Subgroup	Area under the Receiver Operating Characteristic Curve (95% CI)	Optimal Cutoff Value for Variable	Odds Values (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Control eyes (n = 411)					
IOP at baseline	0.60 (0.54–0.66)	> 13 mmHg	2.70 (1.48–4.90)	0.85 (0.77–0.92)	0.31 (0.26–0.37)
Limbal ACD*	0.61 (0.55–0.67)	≤ 15%	2.44 (1.54–3.86)	0.49 (0.39–0.59)	0.72 (0.67–0.77)
Central ACD†	0.63 (0.56–0.69)	≤ 2.44 mm	2.41 (1.51–3.85)	0.44 (0.34–0.54)	0.76 (0.70–0.80)
Above 3 parameters combined	0.70 (0.64–0.76)§	—	—	—	—
LPI-treated eyes (n = 409)					
IOP at baseline	0.62 (0.51–0.72)	> 15 mmHg	2.01 (0.97–4.16)	0.61 (0.42–0.77)	0.57 (0.51–0.62)
Limbal ACD*	0.65 (0.55–0.75)	≤ 15%	3.00 (1.46–6.20)	0.58 (0.39–0.75)	0.69 (0.64–0.74)
IOP changes after DRPPT	0.62 (0.52–0.72)	≤ 4 mmHg	2.45 (1.14–5.29)	0.70 (0.51–0.84)	0.52 (0.46–0.57)
Above 3 parameters combined	0.71 (0.61–0.81)§	—	—	—	—

ACD = anterior chamber depth; CI = confidence interval; DRPPT = darkroom prone provocative test; IOP = intraocular pressure; LPI = laser peripheral iridotomy; — = not available in the multivariable models.
*Evaluated by modified van Herick grading.
†Evaluated by ultrasoud A-scan.
§The area under the receiver operating characteristic curve of multivariable models was significantly higher than those of univariable models in control eyes (all $P < 0.05$). No significant difference was found between the area under the receiver operating characteristic curve of multivariable models and those of univariable models in treated eyes.

Nevertheless, the mere 0.34-mmHg elevation of IOP found in LPI-treated eyes was unlikely to affect established protective effects of LPI as a secondary finding in those without PAC occurrence.

Risk Factors for the Natural Progression of PACS

The higher number of events that occurred over a long follow-up period potentially allowed us to identify those at high risk of progression to PAC. We found that both LACD and CACD were potential risk factors for naturally rapid PACS progression, which is consistent with the results of previous studies. In the Handan Eye Study, logistic regression analysis found that baseline angle width was associated with progression.[14] Another study in a Mongolian population indicated that narrow angles diagnosed by grading LACD and gonioscopy were associated strongly with the occurrence of an occludable angle.[18] Another study including 75 patients with PACS in the Greenland subgroup found that LACD (25%) and CACD (2.7 mm) could discriminate effectively a subgroup that is at risk of PACG developing over 10 years.[19] Previous studies have demonstrated that van Herick examination is highly reproducible between observers, and our prior analysis showed a sensitivity of 98.2% for the diagnosis of PACS with LACD grading at a 25% cutoff.[20] Another important risk factor was baseline IOP, which was consistent with the ANA-LIS study results that eyes with higher IOP were more likely to arrive at the end points.[6]

Risk Factors for PAC Occurrence after LPI

It was reported that 11% to 25% of eyes with PACS remained closed persistently after LPI.[21] In the Liwan Eye Study, 19.4% of PACS eyes remained closed on gonioscopy after LPI treatment, and ultrasound biomicroscopy revealed that 59% of eyes had 1 quadrant or more of iridotrabecular contact.[22,23] In a hospital-based study, about 22% of Vietnamese patients progressed to PAC within an 11-year follow-up after LPI.[24] Another hospital-based study found that approximately 28% of patients with PACS progressed to PAC within 2 years of undergoing LPI.[25] In the ANA-LIS study, 81.8% of participants showed residual angle closure of 2 quadrants or more under gonioscopy at 1 year after LPI, which was related to greater iris volume and higher IOP. Our study further confirmed that patients with lower LCAD and higher IOP at baseline were more likely to demonstrate PAC even after LPI, which represented occludable angles and compromised aqueous humor outflow.[6] Notably, we found that less IOP elevation after DRPPT was an independent risk factor for PAC progression after LPI. Given the fact that DRPPT generally was used to stimulate a pupil block mechanism[26] and LPI removed the pupil block mechanism, the observed marginal statistically significant association between DRPPT and primary end points among LPI eyes likely was spurious. This is consistent with the findings that DRPPT is unable to discriminate patients with PACS from those at risk of PAC progression in the previous studies.[12,27]

Strengths and Limitations

This study has several advantages. First, the split-body design, in which one eye is randomized to treatment and the other eye serves as a control, reduces individual-level confounding factors. Second, the study had a sufficiently long follow-up period to observe the outcomes of the events or events of interest. Third, the sample size of the study was large, and the level of effort required to run such a long-term follow-up trial with high retention rates was substantial. Modeling PACS-treated and LPI-treated eyes separately, we also explored potential risk factors for PAC occurrence.

This study has some limitations. First, patients at high risk for PACS were excluded, such as those with previous episodes of acute attack in either eye or those with DRPPT results of $>$ 15 mmHg. Therefore, the end point rate derived from the trial might underestimate the actual morbidity rate. Second, about 45% of participants dropped out the 14-year follow-up, and quite a few patients underwent cataract surgery. The role of cataract surgery in the management of patients with PACS should be investigated in future randomized controlled trials. Third, the effects of corneal thickness, daytime IOP fluctuations, and family history of PAC on the outcomes were not assessed.[3] Fourth, only the Chinese population was included, and the results cannot be directly generalized to patients of other ethnic groups. Last but not least, efficacy of IOP, CACD, LACD, and DRPPT in the prediction of PAC occurrence was not satisfactory. To improve the predictive performance further, detailed quantification of anterior chamber structures based on anterior segment OCT and ultrasound biomicroscopy is warranted in the future.

Conclusions

In summary, the 14-year ZAP Study demonstrated that LPI significantly reduced the risk of PAC occurrence in PACS eyes by two thirds over the long term, which further confirmed previous 6-year results and supported the suggestion that LPI-free observation is an alternative response to PACS. Considering that the progression rate was relatively low and that most PAC cases were asymptomatic, prophylactic LPI should be prescribed primarily for the high-risk population. Although baseline IOP, IOP change after DRPPT, LACD, and CACD were associated significantly with PAC occurrence in LPI-treated or control eyes, more potent predictors are still needed to realize precise prediction and to guide targeted intervention in the future.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. The extended study was approved by the Zhongshan Ophthalmic Center Ethical Review Committee and performed in accordance with the Declaration of Helsinki. All participants signed informed consent forms before enrollment and each follow-up.

No animal subjects were included in this study.

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Conception and design: Wang, Friedman, Foster, He

Analysis and interpretation: Yuan, Wang, Zhang, He

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Obtained funding: Wang, Foster, Friedman, He

Overall responsibility: Yuan, Wang, Xiong, Zhang, He

Abbreviations and Acronyms:
AAC = acute angle closure; **ACD** = anterior chamber depth; **ANALIS** = Asymptomatic Narrow Angles Laser Iridotomy Study; **CACD** = central anterior chamber depth; **CI** = confidence interval; **DRPPT** = darkroom prone provocative test; **HR** = hazard ratio; **IOP** = intraocular pressure; **LACD** = limbal anterior chamber depth; **LPI** = laser peripheral iridotomy; **NNT** = number needed to treat; **PAC** = primary angle closure; **PACG** = primary angle-closure glaucoma; **PACS** = primary angle-closure suspect; **PAS** = peripheral anterior synechiae; **ZAP** = Zhongshan Angle-Closure Prevention.

Keywords:
Extended follow-up, Laser peripheral iridotomy, Primary angle closure.

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