Laser peripheral iridotomy for the prevention of angle closure: a single-centre, randomised controlled trial

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Summary

Background Primary angle-closure glaucoma affects 20 million people worldwide. People classified as primary angle closure suspects have a higher but poorly quantified risk of developing glaucoma. We aimed to assess efficacy and safety of laser peripheral iridotomy prophylaxis against primary angle-closure glaucoma in Chinese people classified as primary angle closure suspects.

Methods In this randomised controlled trial, bilateral primary angle closure suspects aged 50–70 years were enrolled at the Zhongshan Ophthalmic Center, a tertiary specialised hospital in Guangzhou, China. Eligible patients received laser peripheral iridotomy in one randomly selected eye, with the other remaining untreated. The primary outcome was incident primary angle closure disease as a composite endpoint of elevation of intraocular pressure, peripheral anterior synechiae, or acute angle-closure during 72 months of follow-up in an intention-to-treat analysis between treated eyes and contralateral controls. This trial is registered with the ISRCTN registry, number ISRCTN45213099.

Findings Of 11 991 screened individuals, 889 individuals were randomly assigned from June 19, 2008 (889 treated and 889 untreated eyes). Incidence of the primary outcome was 4·19 per 1000 eye-years in treated eyes compared with 7·97 per 1000 eye-years in untreated eyes (hazard ratio 0·53; 95% CI 0·30–0·92; p=0·024). A primary outcome event occurred in 19 treated eyes and 36 untreated eyes with a statistically significant difference using pair-wise analysis (p=0·0041). No serious adverse events were observed during follow-up.

Interpretation Incidence of angle-closure disease was very low among individuals classified as primary angle closure suspects identified through community-based screening. Laser peripheral iridotomy had a modest, albeit significant, prophylactic effect. In view of the low incidence rate of outcomes that have no immediate threat to vision, the benefit of prophylactic laser peripheral iridotomy is limited; therefore, widespread prophylactic laser peripheral iridotomy for primary angle-closure suspects is not recommended.

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Introduction

Glaucoma is the world's most common neurodegenerative disease, affecting around 80 million people, and is the second most common cause of blindness.[1] Primary angle-closure glaucoma accounts for 25% of all glaucoma globally and it is more visually destructive than the more common variant, primary open angle glaucoma. More than three-quarters of individuals with primary angle-closure glaucoma live in Asia, and 3·1 million Chinese citizens are blind in at least one eye from primary angle-closure glaucoma.[2,3] Primary angle-closure glaucoma is assumed to develop from a larger group of people in whom the drainage of aqueous humour from the eye is impeded by narrowing of the outflow channels in the anterior chamber angle. Individuals in whom half the outflow channels appear obstructed are considered to be at high risk of primary angle-closure glaucoma. These people are termed primary angle closure suspects. Angle closure can be caused by many factors, including the location of the lens, iris thickness and insertion, ciliary body location, and degree of pupil block.[4] Primary angle-closure is an intermediate stage in which ocular anatomy and physiology of the trabecular meshwork are obstructed by the peripheral iris, but vision is normal.[4] More than 28 million people are estimated to be primary angle closure suspects, 9 million are estimated to have primary angle-closure, and 4·5 million are estimated to have primary angle-closure glaucoma in China alone.[2]

Laser peripheral iridotomy has been the first-line treatment for primary angle-closure and primary angle-closure glaucoma since the mid-1970s.[5] Laser peripheral iridotomy is mandatory in acute angle-closure, a clinical variant presenting with florid symptoms.[6] Although widely practiced, evidence for prophylactic laser peripheral iridotomy in primary angle closure suspects is scarce. In the USA, nearly 50 000 laser peripheral iridotomy procedures are done annually.[7] In the UK, where 31·1 million people are aged 40 years and older,[8] incident acute angle closure or primary angle-closure

Research in context

Evidence before this study

We searched for studies published between database inception and June 30, 2018, in English in MEDLINE, PubMed, Embase, and the Cochrane Collaboration Database and hand searched the reference lists of important articles. We identified one systematic review that assessed nine randomised clinical trials and 24 non-randomised clinical trials and large case series. This review concluded that laser peripheral iridotomy should be recommended for treatment of affected and contralateral eyes of patients with acute angle-closure. Evidence was insufficient to advise prophylactic iridotomy for other angle-closure diseases, although this was widespread practice. A Cochrane review examining the benefits of laser iridotomy in management and prophylaxis of angle-closure disease was published on June 13, 2018. This review searched Cochrane CENTRAL (2017, Issue 9), which contains the Cochrane Eyes and Vision Trials Register, MEDLINE Ovid, Embase Ovid, PubMed, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform (search date Oct 18, 2017). This review noted that our trial and one other similar trial in Singapore were ongoing, and that robust data on the benefit of prophylactic laser iridotomy was scarce.

Added value of this study

This large randomised controlled trial provides the first robust evidence on the use of laser peripheral iridotomy as prophylaxis against primary angle-closure disease and associated glaucoma. At the annual data monitoring meeting before all participants completed the 18-month follow-up visit, we decided to extend the study from 36 months to 72 months and enrol additional participants, given the much smaller than predicted event rate. At the 72-month visit, laser peripheral iridotomy-treated eyes had a small but statistically significant benefit, with incidence of primary angle-closure disease in treated eyes of 4·2 cases per 1000 eye-years compared with 8·0 per 1000 eye-years in untreated eyes (hazard ratio 0·53, 95% CI 0·30–0·92).

Implications of all the available evidence

The incidence of angle-closure disease was very low among angle-closure suspects identified through community-based screening. Laser peripheral iridotomy had a modest, albeit significant, prophylactic effect. Most individuals who developed incident primary outcomes had no immediate threat to vision; therefore, the benefit of prophylactic laser peripheral iridotomy was small in this 72-month study. Widespread prophylactic laser peripheral iridotomy for primary angle-closure suspects is not recommended.

glaucoma occurs at around 4 cases per 100 000 population per year (around 1250 cases per year).[9] In 2014–15, 10 284 laser iridotomies were performed in the UK National Health Service, suggesting many were for early-stage disease (most likely primary angle closure suspects).[10] 75% of UK consultant ophthalmologists surveyed in 2000 offered prophylactic laser peripheral iridotomy.[11] In China, which has 28 million primary angle closure suspects, the question of prophylactic treatment raises important questions regarding health economics, opportunity costs, and public health policy. One randomised trial of screening and prophylactic laser peripheral iridotomy for individuals with primary angle closure suspects carried out in Mongolia reported no benefit in prevention of sight loss from glaucoma, although this study suffered considerable loss to follow-up.[12,13] The natural history of primary angle closure suspects is poorly documented owing to the scarcity of long-term observational data.

Although widely practised, the efficacy and safety for prophylactic laser peripheral iridotomy is unclear. The aim of this trial was to assess the efficacy of laser peripheral iridotomy in preventing the development of primary angle-closure or acute angle closure in Chinese people with primary angle closure suspects. Meanwhile, the untreated eyes allowed us to observe the natural history of primary angle closure suspects, because no intervention was applied to these eyes.

Methods

Study design and participants

The full study protocol and planned statistical analysis of this trial have been published previously.[14] Briefly, the Zhongshan Angle Closure Prevention (ZAP) Trial is a single-centre, randomised interventional controlled trial. All examinations and interventions were done in the Clinical Research Center at Zhongshan Ophthalmic Center, a tertiary specialised hospital in Guangzhou, China.

Participants aged 50–70 years from an urban district in Guangzhou were invited to receive a screening examination to identify those eligible. Individuals presenting as bilateral primary angle closure suspects were enrolled. A primary angle closure suspect was defined as an individual with angle closure (≥6 clock hours of angle circumference, in which the posterior, usually pigmented, trabecular meshwork was not visible under non-indentation gonioscopy) in the absence of primary angle-closure or primary angle-closure glaucoma. Specifically, no peripheral anterior synechiae was observed on gonioscopic examination and the intraocular pressure was 21 mm Hg or less (two standard deviations above the norm for urban Chinese populations).[4] The optic nerve was assessed by an ophthalmologist. Eyes were eligible if vertical cup-to-disc ratio was less than 0·7, cup-to-disc asymmetry was no greater than 0·2, and neuroretinal rim width was greater than 0·1 vertical disc diameter with reference to standard

photos. Standard automated perimetry was performed on all enrolled participants and normal or borderline glaucoma hemifield test results were required. Exclusion criteria included severe health problems resulting in a life expectancy of less than 1 year, previous intraocular surgery or penetrating eye injury, media opacity preventing laser peripheral iridotomy, best corrected visual acuity worse than 20/40, or an intraocular pressure increase greater than 15 mm Hg after dilation or after a 15-min dark room prone provocative testing. Recruitment was by means of flyers and television advertisements offering free eye examinations.

This trial was approved by the Ethical Review Board of Sun Yat-Sen University, the Ethical Committee of Zhongshan Ophthalmic Center, and the Moorfields Eye Hospital (via the London School of Hygiene & Tropical Medicine) and Johns Hopkins University institutional review boards. This trial was done in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants before enrolling. The trial was supervised by an independent data monitoring and safety committee, an independent trial steering committee, and an independent advisory committee.

Randomisation and masking

All eligible participants were allocated to receive laser peripheral iridotomy in one randomly selected eye, with the contralateral eye serving as an untreated control. A pre-generated list of random numbers was used to perform randomisation. Each eligible participant was assigned a number according to their sequence of entering the study. Randomisation numbers and their corresponding eye assignment were generated at the data monitoring centre at Wilmer Eye Institute (Baltimore, MD, USA). The random number was kept in a sealed envelope with the corresponding sequential number written on the cover and sent to the clinical data collection centre at Zhongshan Ophthalmic Center. The envelope was opened by a masked research nurse before laser peripheral iridotomy treatment. Enrolment and randomisation was a continuous process that began on June 19, 2008.

Procedures

Laser peripheral iridotomy was done by a trained doctor, per a standard clinical protocol, with the use of an Abraham lens (Ocular Instruments, Bellevue, WA, USA). 15 min after one drop of brimonidine 0·15% and pilocarpine 2%, a YAG laser machine (Visulas YAG III, Carl Zeiss Meditec, Dublin, CA, USA) was used to create an iridotomy starting with an initial setting of 1·5 mJ and titrating as needed to create a patent iridotomy of at least 200 µm in diameter. Wherever possible, the laser peripheral iridotomy was placed in a crypt or other area where the iris appeared thinnest and was positioned beneath the superior lid. All participants received dexamethasone 0·1% eye drops hourly for 24 h and then four-times daily for 1 week after the laser peripheral iridotomy.

Outcomes

Both treated and untreated eyes were examined on follow-up visits after 2 weeks, 6 months, 18 months, 36 months, 54 months, and 72 months. The primary outcome was the incidence of primary angle closure by eyes by 72 months, defined as the composite of three study endpoints: (1) intraocular pressure measurements above 24 mm Hg on two separate occasions; (2) development of at least one clock hour of peripheral anterior synechiae in any quadrant; or (3) an episode of acute angle closure. Secondary outcomes were presenting visual acuity, intraocular pressure, total angle width on gonioscopy, limbal anterior chamber depth, and any adverse events during laser peripheral iridotomy or at any follow-up visits. Although we monitored for the development of glaucoma, it was thought to be unlikely to occur in a substantial number of enrolled participants and, therefore, was not used as a study endpoint.

Gonioscopy was done in a standardised dark environment with low ambient illumination (<1 lux) at all study visits. Static gonioscopy was done using a Goldmann-type, one-mirror gonioscopic lens (Single Mirror Gonioscope, Ocular Instruments, Bellevue, WA, USA) with a 1 mm narrow beam. Angle width was

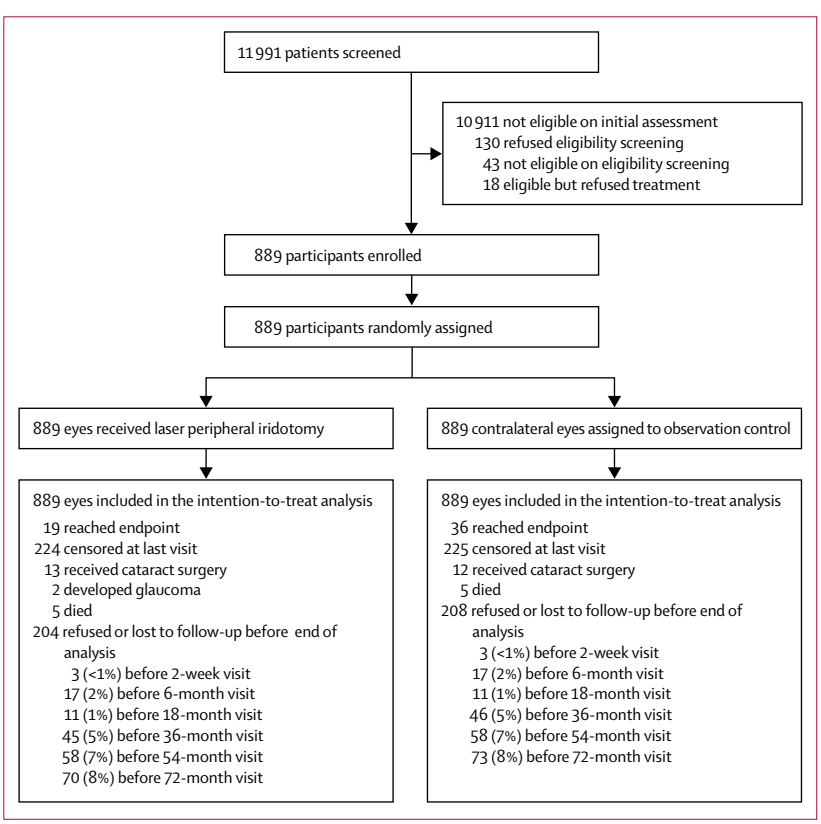

Figure 1: **Study profile**

assessed using the Shaffer grading system. The width of the anterior chamber angle in each quadrant was estimated as the angle in degrees between a tangent line to the surface of the trabecular meshwork and another tangent line to the peripheral third of the iris, and then was recorded in five-point categories (Shaffer grades 0 to 4 correspond to 0°, 10°, 20°, 30°, and 40° angle width, respectively). Sometimes the iris is bowed forward making visualisation of the angle quite challenging and in many of these eyes the angle is open. We allowed slight tilting of the gonioprism towards the angle being examined. We did not allow for greater manipulation, because it could lead to compression opening the angle. If trabecular meshwork was not visible using the single mirror lens, a dynamic examination with a four-mirror gonioscope (Sussman Four Mirror Gonioscope, Ocular Instruments, Bellevue, WA, USA) was done to determine whether peripheral anterior synechiae were present. If iridotrabecular contact was reversible with compression gonioscopy (ie, could be opened and no peripheral anterior synechiae), the patient was considered to be a primary angle closure suspect and was eligible to be included in the study. Gonioscopy was done by glaucoma specialists after training to achieve standardisation (weighted κ values for all gonioscopy variables >0·80 were achieved). If eyes were determined to have reached a primary endpoint, gonioscopic examination was confirmed by a senior glaucoma specialist (MH or PJF).

Presenting visual acuity was assessed for each eye under standard lighting conditions using the Early Treatment Diabetic Retinopathy Study logarithm of the minimum angle of resolution E chart (Precision Vision, Villa Park, IL, USA). The intraocular pressure was measured by non-contact tonometry (Topcon CT-80A, Tokyo, Japan) first, and individuals with intraocular pressure of more than 24 mm Hg in either eye underwent Goldmann applanation tonometry to confirm intraocular pressure elevation. The limbal anterior chamber depth was evaluated by a modified van Herick grading system using a slit lamp (BQ-900, Haag-Streit, Switzerland). Limbal anterior chamber depth was graded clinically, with reference to standard photographs, as the depth of the temporal anterior chamber at the corneoscleral junction, expressed as a percent of the adjacent corneal thickness. Tropicamide 0·5% and phenylephrine 5% were used to dilate the pupil for clinical examination of the lens, disc, macula, and retinal periphery at baseline and at each follow-up visit. Cataracts were graded using the Lens Opacity Classification System III with reference to standard photographs. It consists of six slit lamp images for grading nuclear colour and nuclear opalescence, five retro-illumination images for grading cortical cataract, and five retro-illumination images for grading posterior subcapsular cataract. Any adverse events were recorded in case-report forms and sent to the data monitoring and safety committee.

Statistical analysis

The sample size was calculated for our primary outcomes at 36 months on the basis of previous reports stating a 3-year incidence of endpoints near 20%.[15] Assuming the total incidence of progression to endpoint over 3 years of 18% (equivalent to 6% annually) in untreated eyes and an attrition rate up to 20%, a final target of sample size of 700 individuals was established, which had 80% power with a two-sided error (α=0·05) to detect a difference of 30% in incidence of the study endpoint in 36 months of follow-up. In the sample size estimation, we did not consider pair-wise statistics, such as McNemar's test, because the discordant rates among treated and untreated eyes were unknown. Considering a possible eligible rate of 10% or lower in the screening survey, we planned to recruit about 10 000 citizens aged 50–70 years to undergo screening examinations.

An independent biostatistics and data monitoring centre was set up at the beginning of the study. The ZAP database was transferred to the data monitoring centre on a weekly basis. The data monitoring and safety committee met annually for a comprehensive review of the data and to provide recommendations. At the annual data monitoring meeting before all participants completed the 18-month follow up visit, the decision was made, approved by all members, to extend the study from 36 months to 72 months and enrol an additional 155 participants, given the much lower than predicted event rate. The expected event rate had been based on the small amount of published literature on similar patients. Because laser peripheral iridotomy was (and is) often recommended to primary angle closure suspects, we felt continuation of the study to determine the overall harms and benefits of this practice would be of value. Furthermore, there was reason to believe that early events in the treated eyes might have been related to the iridotomy itself (dispersion of pigment and inflammation); therefore, the outcome might be different over time. Given this interim analysis, we adjusted the significance threshold to a p value of 0·025.

All analyses were based on intention-to-treat principle and included all participants who randomly assigned. Participants who prematurely received laser peripheral iridotomy in the control eye but did not withdraw from the study were followed and analysed according to randomisation (n=24). Data from individuals who underwent cataract surgery were censored at the last visit before cataract surgery.

The prophylactic effects were expressed in pair-wise analyses of the primary outcome using McNemar's test, given that randomisation was at eye-level within an individual to account for inter-eye correlation. Hazard ratios (HRs) with 95% CIs were estimated using a Cox proportional hazards model between treated and untreated eyes. The Cox proportional model was chosen as an additional analysis, because it took into account both time and event; a small number of participants

contributed different follow-up time between two eyes (ie, one eye developed endpoint but not the contralateral eye, or only one eye was censored due to cataract surgery). We used Kaplan-Meier failure curves to display event rates and log-rank tests to test for equality of failure curves. Outcome measurements were compared by the paired *t* test for continuous variables, McNemar's test for nominal variables, and Wilcoxon signed test for ordinal variables (limbal anterior chamber depth score). All statistical analyses were conducted using Stata version 13.1. The significance level was set at 0·025 using a two-side test. This trial is registered with the ISRCTN registry, number ISRCTN45213099.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. DSC, BM, MH, PJF, and DSF had access to all the data in the study. MH, PJF, and DSF had final responsibility for the decision to submit for publication.

	Laser peripheral iridotomy (n=889)	Control (n=889)
Spherical equivalent, diopter	2·11 (1·35)	2·14 (1·37)
Cup-to-disc ratio	0·40 (0·14)	0·40 (0·14)
Axial length, mm	22·49 (0·73)	22·49 (0·72)
Central anterior chamber depth, mm*	2·55 (0·22)	2·55 (0·22)
Lens thickness, mm	4·87 (0·33)	4·88 (0·32)
Goldmann applanation tonometry intraocular pressure, mm Hg		
Before provocative test	14·3 (2·6)	14·3 (2·6)
After provocative test	18·6 (3·2)	18·6 (3·2)
Limbal anterior chamber depth grade, n (%)†		
5%	31 (3%)	32 (4%)
15%	262 (30%)	271 (30%)
25%	557 (63%)	543 (61%)
40%	35 (4%)	38 (4%)
75%	4 (<1%)	5 (<1%)
Total angle width on Gonioscopy, score‡	5·33 (2·37)	5·34 (2·40)
Number of closed quadrants, n (%)		
2 quadrants	36 (4%)	31 (3%)
3 quadrants	114 (13%)	113 (13%)
4 quadrants	739 (83%)	745 (84%)
Lens Opacity Classification System III grading		
Nuclear opacity	2·30 (0·59)	2·30 (0·59)
Nuclear colour	2·17 (0·58)	2·18 (0·58)
Cortical opacity	0·84 (1·16)	0·85 (1·17)
Posterior subcapsular cataract	0·11 (0·30)	0·12 (0·33)

All values are mean (SD) unless stated otherwise. *Measured by ultrasound A-scan. †Evaluated using modified van Herick grading. ‡Total angle width was calculated by the sum of Shafer grading of all four quadrants (range from 0 to 16, larger number indicates wider angle).

Table 1: **Baseline characteristics of laser peripheral iridotomy-treated and control eyes**

Results

11 991 individuals aged 50–70 years underwent screening assessment between June 1, 2008, and Dec 31, 2008. Of the 1087 participants identified as eligible bilateral primary angle closure suspects, 188 declined participation in the trial and 889 were enrolled and treated by laser peripheral (figure 1). The recruitment was completed on Oct 29, 2010. The study was completed on Nov 6, 2016, which provided time for 72-month follow-up visits for all participants.

The mean age of participants at enrolment was 59·3 years (SD 5·0). 737 (83%) of the 889 participants

	Laser peripheral iridotomy (n=889)	Control (n=889)	p value
Reach primary endpoint	19 (4·19 per 1000 eye-years)	36 (7·97 per 1000 eye-years)	0·021
2 weeks	1	1	..
6 months	5	3	..
18 months	5	6	..
36 months	3	6	..
54 months	2	11	..
72 months	3	9	..
Intraocular pressure measures >24 mm Hg	3 (0·66 per 1000 eye-years)	5 (1·11 per 1000 eye-years)	0·480
2 weeks	0	0	..
6 months	1	0	..
18 months	2	2*	..
36 months	0	2*	..
54 months	0	0	..
72 months	0	1*	..
Peripheral anterior synechiae ≥1 clock hour	15 (3·31 per 1000 eye-years)	30 (6·64 per 1000 eye-years)	0·024
2 weeks	0	0	..
6 months	4	3	..
18 months	3	5†	..
36 months	3	5†	..
54 months	2	11	..
72 months	3	6†	..
Acute attack	1 (0·22 per 1000 eye-years)	5 (1·11 per 1000 eye-years)	0·100
2 weeks	1§	1‡	..
6 months	0	0	..
18 months	0	0	..
36 months	0	1§	..
54 months	0	0	..
72 months	0	3	..

All values are number of events unless stated otherwise. p values were estimated by log-rank test for equality of survival function. Six participants reached endpoint in both eyes at the same visit and four reached endpoint in both eyes at two separate visits. *Three control eyes reached both intraocular pressure and peripheral anterior synechiae endpoint at the same visit. †Four control eyes reached both PAS endpoint and IOP or acute attack endpoint at the same visit. ‡Same individual with bilateral acute attack after dilation. §One control eye reached both PAS endpoint and acute attack endpoint at the same visit.

Table 2: **Primary outcomes at 72 months by intention-to-treat analysis**

		Laser peripheral iridotomy		
		No endpoint	Endpoint	Total
Control	No endpoint	844	9	853
	Endpoint	26	10	36
	Total	870	19	889

Figure 2: **Pair-wise analyses of primary endpoint (intention-to-treat analysis) at 72 months**
p=0·0041 with McNemar's test.

See Online for appendix

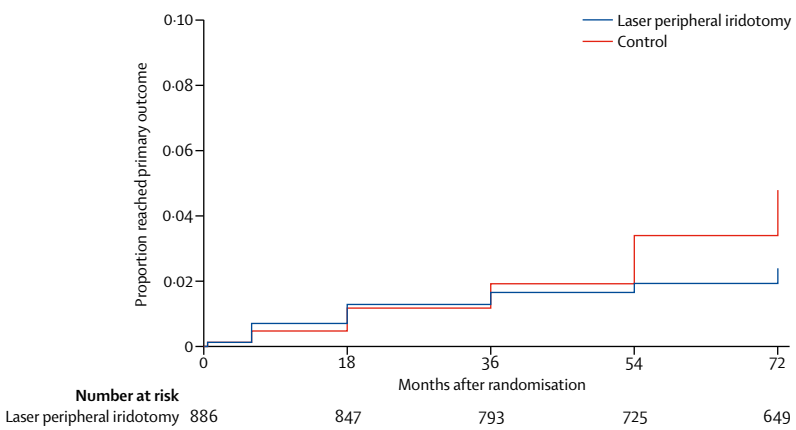

Figure 3: **Kaplan-Meier plot of the study endpoint**

	Eyes that did reach endpoint, n=55, 3%	Eyes that did not reach endpoint, n=1723, 97%	Hazard ratio (95% CI)	p value
Univariate model				
Randomly assigned to laser peripheral iridotomy	34·5%	50·5%	0·53 (0·30-0·92)	0·024
Multivariate models				
Age, years (per 1 year older)	60·91 (5·76)	59·25 (4·97)	1·07 (1·01-1·13)	0·015
Female (*vs* male)	81·8%	82·9%	1·11 (0·55-2·24)	0·765
Randomly assigned to laser peripheral iridotomy (*vs* control)	34·5%	50·5%	0·52 (0·30-0·91)	0·023
Baseline intraocular pressure, mm Hg (per 1 mm Hg increase)	15·76 (3·02)	15·06 (2·83)	1·09 (0·99-1·19)	0·075
Total angle width*, score (per 1 score higher)	4·80 (2·37)	5·36 (2·38)	0·91 (0·82-1·02)	0·098
Limbal anterior chamber depth†, % (per 10% higher)	18·64 (8·41)	22·28 (7·57)	0·49 (0·34-0·71)	<0·001
Central anterior chamber depth‡, mm (per 1 mm deeper)	2·47 (0·24)	2·55 (0·22)	0·21 (0·06-0·72)	0·013
Lens thickness‡, mm (per 1 mm thicker)	4·95 (0·37)	4·87 (0·32)	1·57 (0·65-3·79)	0·318
Dark room prone provocative test, mm Hg (per 1 mm Hg increase)	3·76 (3·39)	4·27 (2·97)	0·94 (0·86-1·03)	0·199

All values are mean (SD) unless stated otherwise. Multivariable Cox proportional hazards models include laser peripheral iridotomy, age, gender, baseline intraocular pressure, and variables of interest. *Total angle width was calculated by the sum of Shafer grading of all four quadrants (range from 0 to 16, larger number indicates wider angle). †Limbal anterior chamber depth was evaluated by modified van Herick grading. ‡Central anterior chamber depth and lens thickness were measured by ultrasound A-scan.

Table 3: **Baseline ocular biometrics and gonioscopic factors associated with endpoint at 72 months**

were female and 152 (17%) were male. The laser peripheral iridotomy-treated eyes consisted of 445 (50%) right eyes and 444 (50%) left eyes. 703 (79%) of laser peripheral iridotomies were placed superiorly, and the rest were placed either nasally or temporally. Baseline demographic measures and other ocular parameters did not differ between the laser peripheral iridotomy-treated and control eyes (table 1).

Mean follow-up for this study was 61·1 months (SD 20·2), 61·2 months (20·3) for the treated group and 61·0 months (20·1) for the control group. 665 (75%) of 889 in the treated group and 664 (75%) of the 889 controls completed the study. 24 control eyes received laser peripheral iridotomy during the study.

During the 72-month follow-up, 19 laser peripheral iridotomy-treated eyes and 36 control eyes reached the primary study endpoint, with a corresponding cumulative incidence of 4·19 per 1000 eye-years (95% CI 2·67–6·57) for treated eyes and 7·97 per 1000 eye-years (95% CI 5·75–11·0) for control eyes (table 2). To account for inter-eye correlation, we analysed the primary outcome using McNemar's test, and the prophylactic effect of laser peripheral iridotomy remained significant (p=0·0041; figure 2) in the pair-wise comparison between treated and untreated eyes. A primary outcome event occurred in both eyes in ten participants (1%; table 2). We did sensitivity analysis by excluding those who did not complete the study, and the findings remained statistically significant (appendix).

We also analysed the primary outcome using Cox proportional hazard model to account for unequal follow up time between two eyes. The laser peripheral iridotomy-treated eyes had a reduction in the risk of reaching an endpoint (HR 0·53, 95% CI 0·30–0·92; p=0·024; figure 3). However, the proportional hazard assumption only held through 36 months of follow-up and laser peripheral iridotomy had no protective effect at that point (HR 0·90, 95% CI 0·44–1·85, p=0·777). The hazard ratio remained similar at 72 months after adjusting for age, sex, baseline intraocular pressure and angle width (HR 0·52, 95% CI 0·30–0·91, p=0·023; table 3). Eyes with narrower angle width at baseline were more likely to develop a study endpoint, but baseline intraocular pressure and dark room prone provocative testing were not associated with reaching an endpoint. The small number of observed events precluded building a predictive model to identify high risk populations; given the low event rate, the study was underpowered to investigate prophylactic effects within subgroups.

Three control eyes and one laser peripheral iridotomy-treated eye developed an acute attack after pupil dilation (one case was bilateral). When these participants were excluded, the HR remained similar between the two groups (HR 0·54, 95% CI 0·31–0·97, p=0·038). Subgroup analysis on each component endpoint demonstrated similar results, with three (0·66 per 1000 eye-years) laser peripheral iridotomy-treated eyes and five (1·11 per 1000 eye-years)

control eyes developing intraocular pressure elevation on two repeated visits, 15 (3·31 per 1000 eye-years) laser peripheral iridotomy-treated eyes and 30 (6·64 per 1000 eye-years) control eyes developing peripheral anterior synechiae of one clock hour or greater, and one (0·22 per 1000 eye-years) laser peripheral iridotomy-treated eye and five (1·11 per 1000 eye-years) control eyes experiencing an acute attack of primary angle-closure (1 laser peripheral iridotomy-treated eye and 3 control eyes after dilation; table 2).

The study was initially designed to last 3 years, but event rates were low and the investigators recognised that there would be insufficient power to draw any conclusions. Before participants completed 18 months of follow-up, the protocol was amended with a revised 72-month endpoint. The Data Monitoring Committee suggested this change on the basis of the low rate of endpoints and raised the possibility of increasing the sample size, extending follow-up, or both. Given the low event rates and our desire to complete the study in a timely fashion we elected to both increase the sample size and extend follow-up. The protocol was updated in the online registry. No difference in outcomes was seen in the larger study population at 3 years despite a small benefit of iridotomy at 6 years (appendix).

At each visit, the laser peripheral iridotomy-treated eyes and control eyes had similar presenting visual acuity and intraocular pressure measurements (table 4). Angles were significantly wider after laser peripheral iridotomy than in untreated eyes; however, 436 (49%) of angles remained closed 2 weeks after laser peripheral iridotomy.[16] For laser peripheral iridotomy-treated eyes, the mean sum of all four Shaffer angle grades increased from 5·3 (SD 2·4) at baseline to 11·5 (3·4) at 36 months, and then decreased to 9·6 (3·4) at 72 months. For control eyes, the total angle width progressively decreased from 5·3 (2·4) at baseline to 3·9 (3·1) at 72 months. No serious adverse events occurred during or immediately after laser peripheral iridotomy treatment (table 5). Localised mild iris bleeding occurred in 257 (29%) of 889 and corneal burns in 1 (<1%) after laser peripheral iridotomy; eight (1%) needed repeat laser peripheral iridotomy treatment (table 5). Only six participants (1%) had an intraocular pressure of 30 mm Hg or more 1 h after laser peripheral iridotomy (table 5), and all were given one drop of brimonidine 0·15% and 25 mg of methazolamide orally. The intraocular pressure of all 6 participants returned to normal 2 h after administration of medications and they were discharged with a prescription of methazolamide 25 mg three times a day for 2 days, at which time the intraocular pressure was rechecked and was normal in all cases. About 10% of participants reported subjective glare, but the size and location of laser peripheral iridotomy were not associated with this symptom.[17] At the end of 72 months, the endothelial cell densities and lens grading were similar between the two groups (table 5).

	Laser peripheral iridotomy	Control	p value
Presenting visual acuity, logarithm of the minimum angle of resolution			
Baseline (n=889)	0·19 (0·17)	0·19 (0·17)	0·908
6 months (n=863)	0·15 (0·15)	0·16 (0·16)	0·016
18 months (n=836)	0·18 (0·16)	0·19 (0·17)	0·017
36 months (n=778)	0·21 (0·18)	0·22 (0·18)	0·093
54 months (n=695)	0·24 (0·18)	0·25 (0·19)	0·244
72 months (n=628)	0·29 (0·21)	0·28 (0·20)	0·121
Intraocular pressure, mm Hg			
Baseline (n=889)	15·07 (2·85)	15·09 (2·83)	0·673
6 months (n=863)	15·89 (2·66)	15·64 (2·64)	<0·001
18 months (n=837)	14·99 (2·71)	14·81 (2·79)	<0·001
36 months (n=777)	15·05 (2·35)	14·86 (2·37)	<0·001
54 months (n=695)	15·76 (2·38)	15·59 (2·33)	<0·001
72 months (n=628)	15·26 (2·47)	15·09 (2·44)	<0·001
Total angle width, score*			
Baseline (n=889)	5·33 (2·37)	5·34 (2·40)	0·858
6 months (n=863)	10·29 (2·82)	4·91 (2·42)	<0·001
18 months (n=837)	9·57 (2·85)	4·53 (2·22)	<0·001
36 months (n=777)	11·47 (3·38)	4·74 (2·99)	<0·001
54 months (n=695)	9·78 (3·59)	3·69 (2·60)	<0·001
72 months (n=628)	9·62 (3·41)	3·93 (3·09)	<0·001
Limbal anterior chamber depth, %†			
Baseline (n=889)	22·17 (7·46)	22·15 (7·78)	0·917
6 months (n=863)	38·33 (16·31)	20·10 (8·15)	<0·001
18 months (n=837)	42·19 (20·75)	19·10 (9·80)	<0·001
36 months (n=777)	38·90 (17·21)	19·05 (9·00)	<0·001
54 months (n=695)	33·16 (14·90)	16·71 (9·46)	<0·001
72 months (n=628)	31·85 (13·59)	17·01 (10·39)	<0·001

Included both eyes without reaching endpoint at each visit. All values are mean (SD). p values were estimated by paired *t* test. *Total angle width was calculated by the sum of Shafer grading of all four quadrants (range from 0 to 16, larger number indicates wider angle). †Limbal anterior chamber depth was evaluated by modified van Herick grading.

Table 4: **Clinical secondary endpoints at each visit**

	Laser peripheral iridotomy (n=889)	Control (n=889)
Immediately after laser peripheral iridotomy		
Localised hyphema, n (%)	257 (29%)	..
Localised corneal burn, n (%)	1 (<1%)	..
Intraocular pressure ≥30 mm Hg, n (%)	6 (<1%)	..
72 months after laser peripheral iridotomy		
Corneal endothelium (cells per mm²), mean (SD)		
Endothelial cell density	2470·51 (308·32)	2484·59 (306·21)
Change in endothelial cell density from baseline	−107·95 (152·24)	−93·20 (134·23)
Cataract Lens Opacity Classification System III, mean (SD)		
Nuclear opalescence	2·87 (0·78)	2·79 (0·69)
Nuclear colour	2·92 (0·79)	2·84 (0·71)
Cortical	0·78 (1·13)	0·81 (1·13)
Posterior subcapsular cataract	0·05 (0·41)	0·05 (0·40)

Endothelial cell density was measured by specular microscopy.

Table 5: **Adverse events**

Discussion

The rate of developing any angle closure endpoint was much lower than expected in primary angle closure suspects' eyes, less than 1% per year. Eyes that underwent laser peripheral iridotomy had a 47% (HR 0·53, 95% CI 0·30–0·92, p=0·024) reduction in the risk of developing primary angle-closure or an acute attack. Laser peripheral iridotomy itself was safe and no long-term adverse events were identified. The majority of endpoints were reached owing to conversion from primary angle closure suspects to primary angle-closure, in particular on the development peripheral angle synechiae, a sign of mild damage from angle closure but not in of itself associated with vision loss. These results argue that prophylactic laser peripheral iridotomy is of modest benefit over the timescale of our trial, given the very low event rate observed and the reduced harm of the majority of endpoints reached.

The low rate of progression from primary angle closure suspects to primary angle-closure was unexpected. Few previous longitudinal studies have addressed the natural progression of primary angle closure suspects and primary angle-closure. In a 5-year Indian cohort study with 82 primary angle closure suspects and 37 people with primary angle-closure, 22% of primary angle closure suspects progressed to primary angle-closure and 28·5% of individuals with primary angle-closure progressed to primary angle-closure glaucoma.[17,18] Among 129 primary angle closure suspects (94% white), 19·4% developed a study endpoint during a mean 2·7-year follow-up in a clinical setting.[19] However, in a community cohort of 485 Chinese individuals with primary angle closure suspects, only 4·1% progressed to primary angle-closure glaucoma over 6 years of follow-up with a progressive reduction of anterior chamber depth occurring in 28% of patients.[20] Another community-based study in Mongolia reported that 1·6% of primary angle closure suspects aged 50 years and older (with or without prophylactic laser peripheral iridotomy) eventually developed primary angle-closure glaucoma in 6 years.[13] Our findings reveal even lower rates of incident disease, with only one in 20 untreated eyes developing primary angle-closure in this time. Of note, the aforementioned studies used varying definitions of angle closure and did not report on standardisation of gonioscopy across graders. We believe that our study results are likely more precise, because the sample enrolled was large with a high retention rate, follow-up was relatively long-term, and all study procedures were done systematically at each visit. If we extrapolate our data to the population of China, among people aged 50 years and older (337 million), in whom 10% (33 million) have primary angle closure suspects, 260 000 people per year will develop primary angle-closure without laser peripheral iridotomy prophylaxis, and this number would be about half as large with iridotomies done uniformly.

The results primarily suggest that the risk of developing primary angle-closure over 6 years is low, but need to be understood in the context of the criteria we chose to define primary angle closure suspects and also how the patients were identified. In this study, we defined primary angle closure suspects on the basis of 6 clock hours or more of the anterior chamber angle having no visible trabecular meshwork on gonioscopy. This definition has been commonly used in most recent studies of angle closure,[21–23] but others have used 270° as the standard.[24–26] If we only selected those participants with 270° or more of angle closure as the enrolment criterion, the incidence of primary angle closure suspects to primary angle-closure would have been effectively the same (4·81% *vs* 4·78%) over 6 years (appendix). The incidence rate of progression was marginally higher for eyes with four quadrants of angle closure at baseline (5·40% over 6 years; appendix). Therefore, the definition of primary angle closure suspects did not affect the finding of a low incidence rate of outcome events. We also did not observe a difference in results when choosing different primary angle closure suspects definitions (HR 0·54, 95% CI 0·31–0·95, p=0·033 for 3 quadrants of angle closure; HR 0·56, 95% CI 0·32–0·98, p=0·044 for all 4 quadrants of angle closure; appendix). Another possible explanation for the low incidence rates could be the use of a community-based sample, which likely selected those who were completely asymptomatic. Most researchers have enrolled clinic patients who might have already been experiencing subclinical angle-closure, leading them to present and resulting in biased results relative to the community at large.

Researchers have attempted to identify other clinical features or examination methods besides gonioscopy, a traditional method for quantifying the degree of angle width, to identify people at increased risk of developing primary angle-closure or primary angle-closure glaucoma. The aforementioned longitudinal studies did not identify any anatomical characteristics as good predictors for identifying individuals likely to develop glaucomatous damage from angle-closure. Furthermore, provocative tests also have not proven effective at predicting outcomes.[27] In our study, we screened all eligible participants with a dark room prone provocative test and only one was excluded from the study before randomisation for an intraocular pressure increase of 16 mm Hg as a safety measure. We also found that the dark room prone provocative test did not help predict which eyes developed primary angle-closure, although this analysis might have been hindered by the small number of incident cases.

Laser peripheral iridotomy-treated eyes had a 47% (HR 0·53, 95% CI 0·30–0·92, p=0·024) reduction in risk of progression to primary angle-closure compared with untreated eyes. Only one of the laser peripheral iridotomy-treated eyes developed an acute attack of angle closure (after protocol-indicated dilation), whereas five did so in control eyes (three after dilation). This finding suggests

that primary angle closure suspects have a small and real risk of an acute attack, and that individuals at risk of developing an acute attack do benefit from laser peripheral iridotomy, but identifying this small subset at baseline is impossible. The overall annual risk reduction was 0·38%; therefore, the number needed to treat was 44 to prevent one case of new primary angle closure disease over 6 years, the vast majority of which were not acute attacks. Assuming that these primary angle-closure cases have a 35% risk of developing sight loss from glaucoma over a further 5 years,[18] and assuming that prevention of sight loss would be the ultimate goal of prophylactic laser iridotomy, then the total number needed to treat (over approximately a decade) would be around 126 people. Given the early nature of most incident primary angle-closure disease in our trial, the number needed to treat would probably be higher. This might make laser peripheral iridotomy non-viable as a strategy for preventing loss of vision in socialised medicine systems or in health insurance systems, where other health interventions might be superior in terms of benefits and costs. That said, given the very low risk, we conclude that efforts to identify and treat with iridotomy on a population basis probably are not the best use of resources, and health-care systems would be more effective if they allocated resources to identifying glaucoma earlier.

We recommend that people classified as primary angle closure suspects be told that the risk of future angle-closure glaucoma is low without laser peripheral iridotomy, but acute angle closure can occur in rare cases and pupil dilation can result in acute angle closure. Programmatic prevention of angle-closure requires a more pragmatic view, and on the basis of the very low risk of developing primary angle-closure, community-based screening to identify primary angle closure suspects and perform laser peripheral iridotomy is not recommended.

One of the major strengths of this study is the fact that laser peripheral iridotomy was done in only one eye, so all other individual-level confounders were controlled for, because each participant acted as their own control. On the basis of previous results, we had planned on a 36-month study but extended it to 6 years due to the small number of eyes converting to primary angle-closure. Additional strengths include low dropout, masked allocation, objective assessment of various parameters, long-term follow-up, and testing in an ethnic group with high risk of primary angle-closure glaucoma. This trial also has limitations. First, due to the nature of the laser peripheral iridotomy procedure, it was not possible to mask the participants and outcome examiners, which could have introduced observational bias. Since peripheral anterior synechiae was a primary endpoint, we did not use anterior segment optical coherence tomography as it probably would have missed peripheral anterior synechiae. Second, gonioscopy is partially subjective variability in gonioscopy grading possibly could have led to non-differential misclassification which would have reduced our ability to detect a real difference if one existed. Finally, the findings from this study are only directly applicable to Chinese (ie, high-risk) individuals of 50 years of age and older with primary angle closure suspects. Other populations might have a different response to iridotomy and additional studies are required.

In summary, incident disease occurred very rarely and, when it did, appeared relatively benign in nature. However, the prophylactic benefit of laser peripheral iridotomy was statistically significant. We estimate 44 people need to be treated to prevent one case of early disease over the subsequent 6 years, with no effect on visual function. Given these findings, we recommend against the widespread practice of laser peripheral iridotomy in primary angle closure suspects based on the current definition. This change in practice will likely save considerable time and money and avoid unnecessary medical interventions. In view of a trial showing superiority of phacoemulsification lens extraction over laser peripheral iridotomy in late stage primary angle-closure and primary angle-closure glaucoma,[28] consideration should be given to focusing resources on identifying these potentially blinding forms of angle-closure and delivering more intensive treatment in a smaller number of patients who are at higher risk of loss of vision.

Contributors

MH, PJF, and DSF conceived and designed the trial. MH, TA, PJF, and DSF were the chief investigators and oversaw the trial throughout. YJ and SH were trial examiners. DSC and BM monitored the data, did analyses, and provided critical feedback to study design and activities. All authors contributed to the interpretation of data, drafting of the report, and decided on its content. All authors approved the final version.

Declaration of interests

We declare no competing interests.

Data sharing

Requests for anonymised individual participant data and study documents will be considered on a case by case basis and on scientific merit by principal investigators and approved by the relevant institutional review boards. In case of disputes, the steering committee will be asked to arbitrate.

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