



### **Ophthalmic Technology Assessment**

# Laser Peripheral Iridotomy in Primary Angle Closure

### A Report by the American Academy of Ophthalmology

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**Purpose:** To examine the efficacy and complications of laser peripheral iridotomy (LPI) in subjects with primary angle closure (PAC).

**Methods:** Literature searches in the PubMed and Cochrane databases were last conducted in August 2017 and yielded 300 unique citations. Of these, 36 met the inclusion criteria and were rated according to the strength of evidence; 6 articles were rated level I, 11 articles were rated level II, and 19 articles were rated level III.

**Results:** Reported outcomes were change in angle width, effect on intraocular pressure (IOP) control, disease progression, and complications. Most of the studies (29/36, 81%) included only Asian subjects. Angle width (measured by gonioscopy, ultrasound biomicroscopy, and anterior segment OCT) increased after LPI in all stages of angle closure. Gonioscopically defined persistent angle closure after LPI was reported in 2% to 57% of eyes across the disease spectrum. Baseline factors associated with persistent angle closure included narrower angle and parameters representing nonpupillary block mechanisms of angle closure, such as a thick iris, an anteriorly positioned ciliary body, or a greater lens vault. After LPI, further treatment to control IOP was reported in 0%-8% of PAC suspect (PACS), 42% to 67% of PAC, 21% to 47% of acute PAC (APAC), and 83%-100% of PAC glaucoma (PACG) eyes. Progression to PACG ranged from 0% to 0.3% per year in PACS and 0% to 4% per year in PAC. Complications after LPI included IOP spike (8–17 mmHg increase from baseline in 6%–10%), dysphotopsia (2%–11%), anterior chamber bleeding (30%–41%), and cataract progression (23%–39%).

Conclusions: Laser peripheral iridotomy increases angle width in all stages of primary angle closure and has a good safety profile. Most PACS eyes do not receive further intervention, whereas many PAC and APAC eyes, and most PACG eyes, receive further treatment. Progression to PACG is uncommon in PACS and PAC. There are limited data on the comparative efficacy of LPI versus other treatments for the various stages of angle closure; 1 randomized controlled trial each demonstrated superiority of cataract surgery over LPI in APAC and of clear lens extraction over LPI in PACG or PAC with IOP above 30 mmHg. Ophthalmology 2018;125:1110-1120 © 2018 by the American Academy of Ophthalmology

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy and safety. After review by members of the Ophthalmic Technology Assessment Committee, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment by the Ophthalmic Technology Assessment Committee/Glaucoma Panel is to examine the efficacy and complications of laser peripheral iridotomy (LPI) in subjects with primary angle closure (PAC).

### Background

Laser peripheral iridotomy is an integral component in the management of PAC. Although LPI has been available since the 1980s, its role in the treatment algorithm for PAC is still debated; questions such as who should be treated with an iridotomy and whether iridotomy prevents disease progression continue to be relevant today. When assessing the literature on LPI for PAC, an important issue is the paucity of studies with controls who were not treated with iridotomy. Another issue is the heterogeneity of study subjects who span the entire spectrum of PAC, ranging from subjects who have iridotrabecular contact (ITC) without any other abnormality, to those who have ITC, peripheral anterior synechiae (PAS),

Table 1. Classification of Primary Angle Closure

Type of PAC	Characteristics
PACS	≥180° of ITC, normal IOP, no PAS, and no optic neuropathy
PAC	≥180° of ITC with PAS or elevated IOP, but no optic neuropathy
PACG	≥180° of ITC with PAS, elevated IOP, and optic neuropathy
APAC or AACC	Occluded angle with symptomatic high IOP

 $\label{eq:AACC} AACC = acute angle-closure crisis; APAC = acute primary-angle closure; IOP = intraocular pressure; ITC = iridotrabecular contact (defined as nonvisibility of posterior trabecular meshwork on static gonioscopy); PAC = primary angle closure; PACG = primary angle-closure glaucoma; PACS = primary angle-closure suspect; PAS = peripheral anterior synechiae.$ 

and optic nerve damage. Because older studies used varying definitions for angle closure and grouped together different stages of angle closure, their results cannot be easily compared and should be interpreted with caution. With the wider use of a classification system that was first proposed by Foster et al in 2002,<sup>3</sup> and subsequently adopted by the American Academy of Ophthalmology's Primary Angle Closure Preferred Practice Pattern (PPP) Guidelines (Table 1),<sup>4</sup> the effect of various treatments for PAC can be better assessed and compared across different studies. The previous Ophthalmic Technology Assessment on LPI,<sup>5</sup> published in 1994, focused mainly on the technical aspects of a then relatively new procedure. The goal of the current assessment is to assess its efficacy and complications in the treatment of PAC.

#### **Questions for Assessment**

The focus of this assessment is to address the following questions: (1) What is the efficacy of LPI? Specifically, what is its effect on anterior chamber angle width, intraocular pressure (IOP) control, and disease progression? and (2) What are the clinically relevant short- and long-term complications of LPI?

### **Description of Evidence**

Literature searches in the PubMed and Cochrane databases, which were originally performed in 2014 and last conducted in August 2017, yielded a total of 300 unique citations. After review by the panel, 36 articles that met the following inclusion criteria were selected: (1) The study reported on outcomes or complications of LPI in patients with PAC; (2) the study contained at least 50 eyes if reporting on short-term outcomes or complications, and the study contained at least 30 eyes with a minimum of 1-year follow-up (or 6 months for acute primary angle closure [APAC]) if reporting on intermediate to long-term outcomes or complications; and (3) the definition of PAC was in accordance with the Academy's Primary Angle Closure PPP guidelines. If the definition of PAC did not meet these guidelines, the Methods section had to provide sufficient detail to reclassify patients into the

categories defined in the PPP (Table 1), namely, PACS, PAC, PACG, and acute angle-closure crisis or APAC. Studies on fellow eyes of APAC were included regardless of the classification scheme used because these eyes are a unique subset in which LPI is known to prevent an acute attack of angle closure. Studies that used Scheimpflug photography to measure angle width were excluded because this technology cannot image the angle recess. Older studies that focused on initial experience with LPI were considered to be not relevant for the purpose of this assessment.

After identifying articles that met the inclusion criteria, the panel methodologist (K.N.-M.) assigned a level of evidence based on the rating scale developed by the Oxford Centre for Evidence-Based Medicine.<sup>6</sup> A level I rating was assigned to well-designed and well-conducted randomized clinical trials; a level II rating was assigned to well-designed case-control and cohort studies and poor-quality randomized trials; and a level III rating was assigned to case series, case reports, and poor-quality cohort and case-control studies. Six articles were rated level I, 11 were rated level II, and 19 were rated level III.

#### **Published Results**

### Studies Evaluating the Effect of Laser Peripheral Iridotomy on Anterior Chamber Angle Width

Various qualitative and quantitative parameters were used to report the effect of LPI on angle width (Table 2). Gonioscopic descriptors included mean Shaffer grade, angle width in degrees, and proportion of eyes with persistent ITC after LPI. The most common imaging-based quantitative parameter reported was the angle opening distance (AOD), the perpendicular distance between the anterior iris surface, and a point 500  $\mu m$  (AOD 500) or 750  $\mu m$  (AOD 750) anterior to the scleral spur.

Seventeen studies 7-23 compared anterior chamber angle width before and after LPI; of these, 11 studies 8-10,13-16,18-20,22 assessed short-term effects with an interval of 1 to 8 weeks between the pre- and post-LPI assessment, 5 studies 7,11,12,17,21 evaluated longer-term effects with an interval of 11 to 37 months between the pre- and post-LPI assessment, and in 1 study, 23 the timing of post-LPI assessment was not specified. The angle was evaluated by gonioscopy in 13 studies, 7,8,10,12,14-19,21-23 by ultrasound biomicroscopy (UBM) in 5 studies, 9,13,14,18,19 and by anterior segment OCT (ASOCT) in 5 studies. 7,10,11,15,20 Six studies used both gonioscopy and imaging (UBM or ASOCT) to evaluate the angle. Of the 13 studies that used gonioscopy, 10 studies 7,8,10,12,15-19,21 reported the change in angle width after LPI, 2 studies 22,23 reported only the proportion of subjects with persistent ITC after LPI, and 1 study 4 only commented on the change in PAS after LPI. All but 3 studies had subjects of Asian origin, including Chinese, Mongolian, Korean, Indian, and Vietnamese.

Short-term Changes in Angle Width. Short-term changes in angle width were evaluated by gonioscopy in 13 studies. The angle width increased in all 10 studies that reported on change in this parameter from before to after LPI (levels II and III). In PACS eyes, the average Shaffer grade was

Table 2. Changes in the Anterior Chamber Angle after Laser Peripheral Iridotomy

Angle-Closure Stage	Author(s), Year	Mean Age (yrs)	Race	Level of Evidence	N	Angle Characteristics	Follow-up	Method of Angle Assessment	Para	nmeter	Before LPI	After LPI	% Change	Persistent Angle Closure
PACS	Jiang et al, <sup>7</sup> 2014	59	Chinese	I	775	ITC ≥180	18 mos	Gonioscopy ASOCT	Angle in degrees Change in AOD 500 Change in ARA		13.5 NA NA	25.7 (2 wks) +54.7 +45.2	+90	25% (ITC ≥180)
	He et al, <sup>8</sup> 2007	67	Chinese	II	72	ITC ≥270	2 wks	Gonioscopy	Mean Shaffer grade	Superior quadrant Inferior quadrant	0.4	1.9 2.8	+375 +211	19% (ITC ≥270)
	He et al, <sup>9</sup> 2007			II			2 wks	UBM	AOD 500 ARA 750 ITC in ≥3 quadrants	menor quadrane	0.067 0.04 48.6%	0.111 0.07 18.1%	+66* +75*	
	How et al, <sup>10</sup> 2012	63	96% Chinese	II	175	ITC ≥180	1 wk	Gonioscopy ASOCT	Mean modified Shaffe AOD 500 ARA	r grade	0.68 0.12 0.13	1.76 0.19 0.17	+159 +58 +31	
	Lee et al, <sup>11</sup> 2013	66	Korean	II	32	ITC ≥270	18 mos	ASOCT	AOD 750 ARA 750		0.17 0.08	0.28 0.13	+65 +63	
	Ramani et al, <sup>12</sup> 2009	52	Indian	III	52	ITC ≥180	24 mos	Gonioscopy	Iris curvature (mm)  Mean modified Shaffe grade in superio inferior quadran	r and	0.34	0.15	-56 +200	
PAC	Dada et al, 13 2007	48	Indian	III	54	ITC ≥180 PAS present	2 wks	UBM	AOD 500 ARA		0.107 0.132	0.208 0.158	+94 +20	
	Lin et al, <sup>14</sup> 2013	60	Chinese	III	66	ITC ≥270 47% had PAS	2 wks	Gonioscopy UBM	Change in PAS (cloc AOD 500	k hours) PAS negative PAS positive	55.5 38.1	-1 +75.1 +42.0	+135 +110	
APAC	Moghimi et al, <sup>15</sup> 2016	61	Iranian	II	52	Mean PAS extent: 70°	6 wks	Gonioscopy ASOCT	Mean Shaffer grade AOD 500 (nasal angl TISA 750 (nasal angl	e)	0.25 0.03 0.028	1.22 0.066 0.054	+388 +120 +93	
	Ahmadi et al, <sup>16</sup> 2017	59	Iranian	II	150	Mean PAS extent: 180°	2 mos	Gonioscopy	Mean Shaffer grade	Superior LPI Inferior LPI	0.68 0.67	0.79 0.83	+95 +16 +24	
	Lim et al, 17 2004	60	84% Chinese	III	44	70.5% had PAS	12 mos	Gonioscopy	Mean Shaffer grade		0.74	1.11	+50	
Fellow eyes of APAC	Ahmadi et al, <sup>16</sup> 2017	59	Iranian	II		Mean PAS extent: 60°	2 mos		Mean Shaffer grade	Superior LPI Inferior LPI	0.81 0.82	0.87 0.95	$^{+7}_{+16}$	
	Gazzard et al, <sup>18</sup> 2003	60	91% Chinese			48% had PAS mean extent 30°	2 wks	UBM	Mean Shaffer grade ARA 750		0.85 3.27	1.67 5.14	+97 +57	33% (ITC ≥270)
	Lim et al, 17 2004	60	84% Chinese			47.7% had PAS	12 mos		Mean Shaffer grade		0.85	1.18 (2 wks) 1.73 (4 mos)	+105	
PACG	Kaushik et al, <sup>19</sup> 2006	51	Indian	III	55	PAS <180	4 wks	Gonioscopy UBM	Mean Shaffer grade  AOD 500: quadrant v	Quadrant with LPI Quadrant opposite LPI vith LPI	0.5 0.6 110.2	1.5 0.7 170.6	+200 +17 +55	
	Dada et al, 13 2007	48	Indian	III	39	PAS ≥180	2 wks	UBM	All parameters		No char		0	
Mixed	Han et al, <sup>20</sup> 2014	61	Korean	II	88	PAC, PACG (No PAS)	2 wks	ASOCT	Proportional change in AOD 750	Cluster 1 Cluster 2	NA NA	NA NA	+116% +46%	
	Nolan et al, <sup>21</sup> 2000		Mongolian	III		PACS, PAC, PACG (ITC ≥270)	11-37 mos	Gonioscopy	Median change in Sh	affer grade		+2		2% (ITC ≥270)
	Peng et al, <sup>22</sup> 2011	66	Vietnamese	III	359	PACS, PAC, APAC, PACG (ITC ≥180)	11.8 yrs	Gonioscopy						11% of PACS 29% of PAC 57% of PACG (ITO ≥180)
	Junqueira et al, <sup>23</sup> 2014	58	Brazilian	III	196	PACS, PAC, APAC, PACG (ITC ≥180, PAS ≤90)	11.4 mos	Gonioscopy						14% (ITC ≥180)

AC = anterior chamber; AOD = angle opening distance (in mm); APAC = acute primary angle closure; ARA = angle recess area (in mm); ASOCT = anterior segment OCT; IOP = intraocular pressure; ITC = iridotrabecular contact; LPI = laser peripheral iridotomy; LV = laser peripheral iridotomy; LV = laser peripheral iridotomy; LV = laser peripheral anterior synechiae; LV

0.7 before LPI and 2.4 after LPI. The change in Shaffer grade (either reported or calculated from available data) ranged from +159% to +375% (4 studies, 1105 eyes). In eyes with PAS, including PAC, PACG, APAC, and fellow eyes of APAC (5 studies, 506 eyes), the average Shaffer grade was 0.7 before LPI and 1.1 after LPI. The change in Shaffer grade ranged from +7% to +388%. Six of the 13 studies that used gonioscopy reported persistent angle closure after LPI ranging from 2% to 57% across the PAC spectrum. The proportion of eyes with persistent angle closure in each of the subgroups was 11% to 25% for PACS, 29% for PAC, 33% for fellow eyes of APAC, 57% for PACG, and 2% to 14% for a mixed group representing all stages of angle closure.

Short-term changes in angle width were evaluated in 6 studies using UBM and ASOCT. Quantitative angle-width parameters obtained using UBM and ASOCT also increased after LPI in all studies except for 1 in which 1 subgroup of patients with PACG and 180° or more PAS showed no change in angle width parameters by UBM. Nine of 10 studies reported on the change in AOD 500/750. In eyes without PAS, including PACS, and PAC/PACG without PAS (5 studies, 403 eyes), AOD increased by 46% to 135%. In eyes with PAS less than 180°, including PAC and PACG (4 studies, 234 eyes), AOD increased by 47% to 110%, and in eyes with PAS greater than 180° (1 study, 39 eyes with PACG), there was no change in AOD.

Long-term Changes in Angle Width. Long-term changes in angle width were studied up to 18 months after LPI in 2 prospective studies (level I and II) on PACS eyes. <sup>7,11</sup> In both studies, a significant decrease in angle width over time was noted in the duration between 2 weeks and 18 months after LPI. One of these studies (level I), the Zhongshan Angle Closure Prevention study, <sup>7</sup> was a randomized controlled trial (RCT) in which 1 randomly selected eye of 775 Chinese PACS subjects was treated with LPI and the fellow eye acted as the control. The longitudinal decrease in angle width over 18 months was more rapid in untreated eyes when compared with eyes treated using LPI ( $P \le 0.003$  for all variables). One prospective study <sup>17</sup> (level III) on fellow eyes of APAC reported that PAS noted at baseline before LPI remained stable during the 12-month follow-up after LPI.

Factors Associated with Persistent Angle Closure after Laser Peripheral Iridotomy. Baseline (pre-LPI) factors that were associated with persistent angle closure after LPI were the presence of PAS; increased IOP; UBM parameters such as shallower peripheral angle width, thicker iris, and more anteriorly positioned ciliary body; and ASOCT parameters such as greater mean lens vault and thicker iris. These factors represent a narrower angle before LPI and nonpupillary block mechanisms of angle closure.

## Studies Evaluating Intraocular Pressure Control after Laser Peripheral Iridotomy

The studies reporting on IOP control are summarized in Table 3 and grouped according to the following subcategories: PACS, PAC, APAC, PACG, and mixed group. The most commonly reported outcomes related to IOP control were IOP elevation above 21 mmHg, the need for further treatment of any type after LPI, and the

need for further glaucoma surgery after LPI. The factors associated with IOP elevation and the need for additional treatment after LPI are listed in Table 4.

Primary Angle-Closure Suspect (4 Studies, 392 Eyes). In 3 studies, <sup>12,21,24</sup> 153 PACS eyes did not have IOP elevation after LPI over a mean follow-up ranging from 11 to 46 months. Peng et al<sup>22</sup> (level III) reported IOP elevation above 21 mmHg in 18% of 239 PACS eyes at a mean interval of 56 months after LPI; 7% required further treatment after LPI and 0.4% required glaucoma surgery.

Primary Angle Closure (4 Studies, 208 Eyes). One short-term prospective study<sup>33</sup> (level II) evaluated IOP responses to various provocative tests before and 1 month after LPI in 50 PAC eyes with PAS but without IOP elevation. All patients also had ultrasound biometry and UBM. An increase in IOP of 6 mmHg or above from baseline was considered to be a positive result. A positive mydriatic provocative test occurred in 26% before LPI and 15% after LPI. The eyes that remained positive on the mydriatic test after LPI had a significantly thicker lens (P = 0.02), decreased trabecular-ciliary process distance (P = 0.014), and narrower trabecular-iris angle (P = 0.048).

In 3 retrospective studies (level III) of PAC eyes (pooled n=158), further treatment (of any type) after LPI was required in 42%, <sup>22</sup> 56%, <sup>25</sup> and 67%, <sup>24</sup> and the follow-up duration in these studies was 12 years, 50 months, and 46 months, respectively. Further treatment after LPI consisted mainly of medical therapy, and relatively few patients required glaucoma surgery (0%–13%).

Acute Primary Angle Closure (5 Studies, 246 Eyes). Four studies 17,26,28,29 (156 eyes) reported IOP elevation after LPI in 21% to 47% of eyes. The interval between LPI for APAC and IOP elevation was 6 months or less in most of the subjects. One of these studies<sup>26</sup> (level I) was an RCT in which Chinese patients with APAC were randomized to receive early phacoemulsification or LPI after the acute attack had been aborted by medical treatment. Follow-up was continued for 18 months after intervention. The authors stated that phacoemulsification was performed "within days of abortion of APAC attack, as soon as the IOP decreased to below 21 mmHg and the inflammation had settled sufficiently for safe intervention." The average time between abortion of attack and phacoemulsification was  $6\pm3$  days. Complications in the phacoemulsification group were intraoperative corneal edema (12/31, 39%), posterior capsular rupture (1/31, 3%), intraoperative bleeding from iris root (1/31, 3%), postoperative fibrinous anterior chamber reaction (5/31, 16%), and visually significant posterior capsular opacification (5/31, 16%). In the LPI group, 1 of 31 eyes (3%) had closed iridotomy and 3 of 31 eyes (10%) had small iridotomies requiring retreatment. In the LPI arm of the study (n = 31 eyes), the prevalence of an IOP rise above 21 mmHg was 32% and 47% at 6 and 18 months, respectively. In contrast, only 1 eve (3.2%) in the phacoemulsification arm (n = 31 eyes) of the study had IOP rise above 21 mmHg at all follow-up time points. Factors associated with IOP rise were treatment by LPI (hazard ratio, 14.9; P = 0.009) and maximum IOP at presentation above 55 mmHg (hazard ratio, 4.1; P = 0.017). Medical therapy was initiated in all eyes with an IOP above

Table 3. Intraocular Pressure Elevation, Need for Further Intervention, and Progression of Angle Closure Disease after Laser Peripheral Iridotomy

Angle- Closure Stage	Author(s), Year	Mean Age (yrs)	Race	Level of Evidence	· N	Angle Characteristics	Follow-up	% With IOP Elevation after LPI	Timing of IOP Elevation after LPI	Progression	% Requiring Any Treatment after LPI (Med/Laser/ Surgery)	% Requiring Escalation of Medical Treatment after LPI	Further Glaucoma Surgery
PACS	Nolan et al, <sup>21</sup> 2000	65% ≥60	Mongolian	III	74	ITC ≥270	11-37 mos	0		0	0		
	Pandav et al, <sup>24</sup> 2007	59	Indian	III	27	ITC ≥180	45.6 mos	0		0		0	0
	Ramani et al, 12 2009	52	Indian	III	52	ITC ≥180	2 yrs	0		29% to PAC	0		0
	Peng et al, 22 2011	66	Vietnamese	III	239	ITC ≥180	11.8 yrs	18	56 mos	22% to PAC	7		0.4%
										4% to PACG			
PAC	Pandav et al, <sup>24</sup> 2007	59	Indian	III	43	ITC ≥180	45.6 mos			9% to PACG	67	9	0
	Peng et al, <sup>22</sup> 2011	66	Vietnamese	III	99	ITC ≥180	11.8 yrs			5% to PACG	42		8%
	Rao et al, <sup>25</sup> 2013	60	Indian	III	16	ITC ≥180	50 mos			0	56		13%
APAC	Lam et al, <sup>26</sup> 2008	69	Chinese	I	32		18 mos	47		0	47		0
	Lim et al, <sup>17</sup> 2004	60	84% Chinese	III	44		12 mos	43	Within 4 mos in 79%		43		
	Aung et al, <sup>27</sup> 2004	62	87% Chinese	III	90		6.3 yrs			48% to PACG			38%
	Lai et al, 28 2006	67	Chinese	III	38		16.4 mos	32	3.1 mos	0	32		0
	Tan et al. <sup>29</sup> 2009	60	93% Chinese	III	42		27.3 mos	21	11.9 mos	19% to PACG	21		19%*
Fellow eyes of APAC	Friedman et al, <sup>30</sup> 2006	62	87% Chinese	III	70		6.3 yrs			7% to PACG			8%
PACG	Pandav et al, <sup>24</sup> 2007	59	Indian	III	33	ITC ≥180	45.6 mos			24% worsened		12	12%
	Chen et al, 31 2008	72	Taiwanese	III	130	ITC >180	24 mos	93	1.1 mos	•	93		41%
	,							83	1.8 mos		83		20%
	Peng et al, 22 2011	66	Vietnamese	III	21	ITC ≥180	11.8 yrs				100		43%
	Rao et al, <sup>25</sup> 2013	60	Indian	III	68	ITC ≥180	50 mos				87		35%
Mixed	Azuara-Blanco et al, <sup>32</sup> 2016		69% "non-	Ī	211	ITC ≥180	3 yrs			15% had VF	65 <sup>†</sup>		11%
			Chinese"	-		_	,			progression			
	Nolan et al, <sup>21</sup> 2000	65% ≥60	Mongolian	III	90	ITC ≥270	11-37 mos			3% of PAC <sup>‡</sup> to PACG	13		10%

APAC = acute primary angle closure; GON = glaucomatous optic neuropathy; IOP = intraocular pressure; ITC = iridotrabecular contact; LPI = laser peripheral iridotomy; PAC = primary angle closure; PACS = primary angle-closure suspect; PACG = primary angle-closure glaucoma; PACS = primary angle-closure glau

<sup>\*</sup>Seven of 8 eyes underwent combined phacoemulsification and trabeculectomy, with a visually significant cataract being the indication for surgery; 1 eye underwent combined phacoemulsification and aqueous drainage device.

<sup>†65%</sup> required medications for IOP control.

<sup>&</sup>lt;sup>‡</sup>One PAC eye described as also having pseudoexfoliation.

Table 4. Factors Associated with Intraocular Pressure Elevation, Need for Further Intervention, and Progression of Angle Closure Disease after Laser Peripheral Iridotomy

Study	Outcome	Associated Factor(s)
Lam et al, <sup>26</sup> 2008	IOP elevation after LPI for APAC	Treatment with LPI (vs. phacoemulsification; HR, 14.9) and maximum IOP at presentation (HR, 4.1)
Rao et al, <sup>25</sup> 2013	Additional IOP-lowering therapy after LPI	Higher baseline IOP and highest IOP before LPI
Nolan et al, <sup>21</sup> 2000	Additional surgery after LPI	C:D ratio $\geq$ 0.8 and IOP $>$ 19 mmHg <sup>21</sup>
Rao et al, <sup>25</sup> 2013	Additional surgery after LPI	Greater extent of PAS at presentation and greater C:D ratio <sup>25</sup>
Chen et al, <sup>31</sup> 2008	Additional surgery after LPI	History of APAC <sup>31</sup>
Ramani et al, 12 2009	Progression from PACS to PAC	Decreased AC angle by UBM
Pandav et al, <sup>24</sup> 2007	Progression from PAC to PACG and worsening of PACG	Presence of $\geq$ 2 quadrants of angle closure at baseline (RR, 13.0) and family history of glaucoma (RR, 2.8)
Tan et al, <sup>29</sup> 2009	Progression from APAC to PACG	Duration of symptoms before APAC and time taken to abort APAC
Peng et al, <sup>22</sup> 2011	Progression in PACS	Cataract surgery was protective

AC = anterior chamber; APAC = acute primary angle closure; C:D = cup-to-disc; HR = hazard ratio; IOP = intraocular pressure; LPI = laser peripheral iridotomy; PAC = primary angle closure; PACG = primary angle-closure glaucoma; RR = risk ratio; UBM = ultrasound biomicroscopy.

21 mmHg, and none of the eyes required cataract or glaucoma surgery during the study period.

Five studies reported on surgical intervention (glaucoma or cataract surgery) after LPI for APAC; 2 RCTs<sup>26,28</sup> (level I and III) reported that none of 70 eyes required surgery after LPI, 1 study<sup>29</sup> (level III) reported cataract surgery in 12 of 42 eyes (29%) and combined cataract and glaucoma surgery in 8 of 42 eyes (19%), and 1 study<sup>27</sup> (level III) reported trabeculectomy in 34 of 90 eyes (38%).

Primary Angle-Closure Glaucoma (3 Studies, 219 Eyes). In 3 retrospective studies  $^{22,25,31}$  (level III), 83% to 100% of PACG eyes required further treatment (of any type) after LPI, and 20% to 43% required further glaucoma surgery after LPI. Glaucoma surgery was more common in PACG eyes with a history of APAC than in eyes without (41% [11/27] vs. 20% [21/103], respectively; P = 0.02). Factors associated with the need for surgery in PACG eyes were higher cup-to-disc ratio and a greater extent of synechial angle closure at presentation.

Mixed Group: Primary Angle Closure and Primary Angle-Closure Glaucoma (2 Studies, 301 Eyes). In 1 study<sup>21</sup> (level III) conducted in Mongolia, 13% of 90 eyes with PAC (defined as ITC ≥270 with IOP >19 mmHg or PAS or signs of prior angle closure) and PACG (defined as ITC  $\geq$ 270 and glaucomatous optic neuropathy, IOP was not a criterion for diagnosis) required further treatment 10 to 37 months after LPI. Ten percent required glaucoma surgery. In contrast, the EAGLE study<sup>32</sup> (level I), a multicenter RCT, reported that 65% of 211 PAC and PACG eyes required medical therapy, and 11% underwent additional glaucoma surgery over a 3-year follow-up period after LPI. In this RCT, LPI and topical medical treatment (standard treatment) were compared with clear lens extraction (CLE) with a monofocal IOL in 419 subjects who had newly diagnosed PACG and at least 1 IOP reading above 21 mmHg (63%) or PAC with an IOP above 30 mmHg (37%). All subjects had at least 180° ITC (appositional or synechial), but notably the extent of synechial closure was not reported in 59%. At 36 months' follow-up, CLE showed greater efficacy in IOP control than LPI showed. In the LPI group (n = 211), 65% required 1 to 4

medications and 11% underwent additional glaucoma surgery. In contrast, 25% of the CLE group (n = 208) were on 1 to 4 medications and only 1 subject (0.5%) required additional glaucoma surgery. Complications were few and included posterior capsular rupture (1% in CLE), irreversible loss of vision of more than 10 Early Treatment Diabetic Retinopathy Study letters (1% in the LPI group and 0.5% in the CLE group), malignant glaucoma (1% in LPI, 0.5% in CLE), macular edema (0.5% in LPI, 2.4% in CLE), and corneal edema (none in LPI, 0.5% in CLE).

### Studies Evaluating Disease Progression after Laser Peripheral Iridotomy

The studies that evaluated disease progression are grouped under the subcategories of PACS, PAC, APAC, fellow eyes of APAC, PACG, and mixed group (Table 3). Progression from PACS to PAC was based on the development of PAS or elevated IOP. Progression from PACS or PAC to PACG was defined using both structural (disc appearance) and functional (visual field) criteria in most studies. The factors associated with disease progression after LPI are listed in Table 4.

Primary Angle-Closure Suspect (4 Studies, 392 Eyes). In  $2^{21,24}$  (level III) of 4 studies that reported on disease progression after LPI, none of 101 PACS eyes progressed over a follow-up duration of 11 to 46 months. In 1 study from India<sup>12</sup> (level III), progression to PAC was reported in 29% of 52 eyes based on the development of PAS; none had IOP elevation, and none developed PACG during the follow-up period of 2 years. A wider anterior chamber angle by UBM was associated with a smaller risk for progression from PACS to PAC (95% confidence interval, 0.703–0.989, P=0.037). Peng et al<sup>22</sup> (level III) reported the longest mean follow-up of 12 years, and over this period 22% of 239 Vietnamese eyes progressed to PAC (based on IOP elevation in 80%) and 4% progressed to PACG. Of note, none of these 4 studies included an untreated control group.

Primary Angle Closure (4 Studies, 225 Eyes). Four studies (level III) evaluated progression from PAC to PACG.

In 1 study, <sup>25</sup> none of 16 eyes progressed over a mean followup period of 50 months. In the remaining 3 studies, the calculated rate of PACG per year was 0.4% (Peng et al, 5% over 12 years), <sup>22</sup> 1% (Nolan et al, 3% over 37 months), <sup>21</sup> and 4% (Panday et al, 9% over 46 months). <sup>24</sup>

Acute Primary Angle Closure (2 Studies, 132 Eyes). In 2 studies (level III) from Singapore, the progression rate to PACG after APAC was reported to be 48% in 90 eyes<sup>2</sup> and 19% in 42 eyes.<sup>29</sup> In the study with the higher progression rate,<sup>27</sup> subjects had symptoms for 3 or more days before presentation, and it was not known if subjects had glaucomatous damage preceding the attack. In addition, details of treatment in the interval between APAC and the study examination 4 to 10 years later were not available, and patients could have been undertreated in this period. In contrast, in the study with the lower progression rate,<sup>2</sup> subjects had a shorter duration of symptoms (mean, 28 hours) before presentation and none of the eyes had glaucomatous optic neuropathy at presentation. Furthermore, 50% of eyes had undergone cataract extraction during the study period, which is likely to have had a favorable effect with respect to disease progression.

Fellow Eyes of Acute Primary Angle Closure (1 Study, 70 Eyes). In the same study population of APAC described in Aung et al,<sup>27</sup> the fellow eyes underwent LPI within 1 week of presentation with APAC, and these were separately evaluated by Friedman et al<sup>30</sup> (level III). Definite or probable glaucoma was present at the time of APAC diagnosis in 2.5% of fellow eyes and developed in an additional 7% over a mean follow-up of  $6\pm 2$  years.

Primary Angle-Closure Glaucoma (1 Study, 33 Eyes). One retrospective study<sup>24</sup> (level III) of Indian subjects with PACG reported that 76% of 33 PACG eyes remained stable and 24% had disease progression over a mean follow-up of 46 months. Progression was defined broadly as worsening of disc or visual field parameters, or additional treatment (medical or surgical) for IOP control. Of the 8 eyes that progressed, half were managed by escalating medical therapy and the other half underwent glaucoma surgery.

Mixed Group: Primary Angle Closure and Primary Angle-Closure Glaucoma (1 Study, 211 Eyes). In the EAGLE study<sup>32</sup> (level I), 15% of 211 eyes in the standard care group (LPI with or without topical medications) were reported to have visual field deterioration (criteria not defined). There was no difference in the number of individuals with visual field deterioration in the standard care versus CLE groups (odds ratio, 0.77; 95% confidence interval, 0.38–1.55).

### Studies Evaluating Complications after Laser Peripheral Iridotomy

The complications after LPI reported in the studies reviewed in this Ophthalmic Technology Assessment include the following: IOP spikes (at least an 8 mmHg increase from baseline in 6% to 10%, IOP >21 mmHg in 2%-72%), dysphotopsia (2%-11%; less with temporal vs. superior LPI, no difference between superior and inferior LPI), anterior chamber bleeding (in 30%-41%, more common with superior than inferior LPI, no difference whether

patients were on antithrombotic therapy [ATT] or not, no difference between superior versus temporal locations), and cataract progression (in 23%–39% over a follow-up period ranging from 1–6 years).

Intraocular Pressure Spikes. Intraocular pressure elevation defined as a specified increase (8–17 mmHg) from baseline IOP immediately after LPI occurred in 6% of patients (4/66)<sup>34</sup> (level III), 10% of eyes (7/72)<sup>8</sup> (level II), and 10% of eyes (72/734)<sup>35</sup> (level I) in 3 studies (Table 5). In 2 of these 3 studies, brimonidine was used to prevent IOP spikes; in the study that did not use brimonidine, IOP elevation was reported in 10% of eyes.<sup>8</sup>

Elevated IOP immediately after LPI was defined as IOP above 21 mmHg in 2 studies (level II), and it occurred in 2% (4/230 eyes)<sup>36</sup> and 64% (191/300 eyes).<sup>16</sup> Brimonidine was used before LPI in the study with the lower frequency of IOP elevation.<sup>36</sup>

Dysphotopsia. Vera et al<sup>37</sup> (level I) conducted a randomized, single-masked, paired-eye, comparative trial to assess the effect of LPI location on the occurrence of dysphotopsia after LPI. A total of 169 PAC/PACS patients who were randomized to receive LPI temporally in 1 eye and superiorly in the other were analyzed. Both LPIs were performed sequentially on the same day, and a questionnaire on symptoms of visual disturbance was completed before LPI and 1 month after LPI. Before LPI, linear dysphotopsias were present in only 0.9% of eyes. After LPI, new-onset linear dysphotopsia was reported more often in eyes with superior LPIs (11%) than in eyes with temporal LPIs (2%, P = 0.002). In eyes with superior LPIs, 7% reported linear dysphotopsia despite the LPI being completely covered by the upper eyelid.

Two other studies that evaluated complications after LPI reported glare or ghost images in 2% of 132 eyes with mostly temporal LPIs (retrospective study)<sup>34</sup> (level III) and glare or "line in vision" in 4% of 300 eyes of 150 patients in an RCT who were randomized to superior LPI in 1 eye and inferior LPI in the other (level II). A standardized questionnaire on visual disturbances was administered at the follow-up visits after LPI, and there was no significant difference in visual symptoms between the superior and inferior LPI locations. <sup>16</sup>

Congdon et al<sup>38</sup> (level I) compared 217 Chinese PACS subjects 18 months after LPI with 250 age- and gendermatched controls. The PACS subjects were a convenience sample chosen from the Zhongshan Angle Closure Prevention study. Glare was evaluated both subjectively (visual symptoms) and objectively (retinal stray light measurement), and for both measures there was no difference between the LPI group and controls. Prevalence of glare did not differ on the basis of the LPI location relative to the eyelid. The long duration of 18 months between LPI and glare assessment may have affected the results in this study.

Anterior Chamber Bleeding. In the RCT by Ahmadi et al<sup>16</sup> (level II), hyphema was reported in 41% of 150 eyes with superior LPI and 30% of 150 eyes with inferior LPI. The difference was statistically significant (P=0.004). In the RCT by Vera et al<sup>37</sup> (level I), there was no difference in intraoperative hemorrhage between superior and temporal LPIs (9% vs. 10%; P=0.71). In the retrospective study by Waisbourd et al<sup>34</sup> (level III), hyphema was reported in 3%

APAC = acute primary angle closure; IOP = intraocular pressure; LPI = laser peripheral iridotomy; PACS = primary angle-closure suspect; ZAP = Zhongshan Angle Closure Prevention

Table 5. Intraocular Pressure Spike Immediately after Laser Peripheral Iridotomy

No. Treated for IOP Spike	14/72 eyes, 19% All eyes with elevated IOP were treated per study protocol.	4/734, 0.5% Eyes with IOP $\geq$ 30 mmHg were treated.	6/66 patients, 9% Criteria for using IOP- lowering treatment not specified.	Not reported 4/230 eyes, 2% All eyes with elevated IOP were treated per study protocol.
No. with IOP Spike after LPI	7/72 eyes, 10%	72/734 eyes, 10%	4/66 patients, 6%	191/300 eyes, 64% 4/230 eyes, 2%
Definition of IOP Spike	10—17 mmHg increase from baseline	≥8 mmHg increase from baseline	>10 mmHg increase from baseline	>21 mmHg >21 mmHg
Interval between LPI and IOP Check (hrs)	1	1	0.5-2	1
Treatment to Prevent IOP Spike	None	Brimonidine before LPI	Brimonidine before and after LPI	None Brimonidine before LPI
Stage of Angle Closure	PACS	PACS	Mixed (77% PACS)	APAC and fellow eyes PACS
Study	He et al, <sup>8</sup> 2007 Liwan Eye Study	Jiang et al, <sup>35</sup> 2012 ZAP study	Waisbourd et al, <sup>34</sup> 2016 (bilateral same-day LPI)	Ahmadi et al, <sup>16</sup> 2017 Kumar et al, <sup>36</sup> 2013

of 66 patients who underwent bilateral same-day LPI, and the position of the LPI was reported as "most often at the 3 or 9 o'clock position." Golan et al<sup>39</sup> (level II) prospectively evaluated the effect of ATT on the incidence of anterior chamber bleeding after superior LPI in 208 eyes of 104 Israeli PACS subjects. Subjects underwent LPI in the right eye while continuing ATT, and the left eye underwent LPI weeks after discontinuing ATT. Antithrombotic medications included aspirin (49%), warfarin (33%), and clopidogrel (18%). The incidence of anterior chamber bleeding was similar whether the patient was on or off ATT (35% in each group). Most patients had minor bleeding that could be stopped with light pressure on the iridotomy lens. The severity of bleeding did not differ between the 2 groups or between different antithrombotic medications. There was a significant correlation between right and left eye bleeders in that most patients who bled in the right eye (while on ATT) also bled in the left (when off ATT). Also, most patients who did not bleed while on ATT also did not bleed when off ATT. These results suggest that ATT need not be discontinued before LPI, and that specific patients may have a bleeding tendency regardless of the medications taken.

Cataract Progression. Vijaya et al<sup>40</sup> (level II) compared the risk of cataract progression in 190 PACS subjects 6 years after LPI with a control group of 3015 subjects who had not undergone LPI. All subjects were part of the Chennai Eye Disease Incidence Study in which a population-based sample of South Indians was reexamined 6 years after a baseline examination. Cataract progression was defined as a change of 2 or more units on the Lens Opacities Classification System II grading scale or a history of cataract surgery in the interval between baseline and follow-up examinations. The risk of cataract progression was significantly greater in the post-LPI subjects (odds ratio, 1.7; 95% confidence interval, 1.3—2.4); progression occurred in 39% of eyes that had undergone LPI versus in 23% of eyes that did not have LPI (P < 0.001).

Lim et al<sup>41</sup> (level III) reported that cataract progression after LPI occurred in 23% of 60 fellow eyes of APAC, and Tan et al<sup>29</sup> (level III) reported progression in 38% of 42 APAC eyes. The follow-up durations in these studies were 27 months and 12 months, respectively, and there was no control group to assess the natural progression of lens opacification. Cataract progression was defined as an increase in the Lens Opacities Classification System II or III grading by 2 or more units on any lens region. An additional criterion was a decrease in best-corrected visual acuity of 2 or more lines.<sup>29</sup>

Change in Endothelial Cell Count. In 1 prospective study<sup>36</sup> (level II) of 230 PACS subjects who underwent LPI in 1 eye, the endothelial cell density decreased from baseline to 3 years after LPI in both treated (-2%) and control eyes (-0.9%), and there was no difference between the 2 groups. In another retrospective study<sup>42</sup> (level III), changes in endothelial cell count (ECC) were investigated in APAC eyes treated with LPI (n = 32) or phacoemulsification (n = 16 eyes). In both groups, the ECC progressively decreased from baseline, with the LPI group showing a significantly greater decrease than the phacoemulsification group at the 12-month (19% vs. 7%) and 24-month follow-ups (23% vs. 13%). The decrease in ECC in the

study of APAC subjects was expectedly higher than that reported in the study on PACS subjects.<sup>36</sup>

Other Complications. The proportion of patients requiring repeat LPI was reported in 5 studies 8,26,33-35 and ranged from 1% (8/734 eyes) at 2 weeks after initial LPI (Jiang et al, 35 level I) to 20% (13/66 patients) within 6 months of the initial treatment (Waisbourd et al, 34 level III). Longer-term patency of LPI was reported in 2 other studies. Nolan et al 21 (level III) found that 98% (157/160) of iridotomies were patent when examined 10 to 35 months later, and Ahmadi et al 16 (level II) reported that 100% of 300 eyes had patent iridotomies 1 year after the procedure.

Inflammation after LPI was reported in 2 studies. The EAGLE study<sup>32</sup> (level I) reported inflammation after LPI in 0.5% (1/211 eyes) that underwent LPI; the severity and duration of inflammation were not specified. Ahmadi et al<sup>16</sup> reported uveitis of grade 2+ and higher in 69% (208/300 eyes) and stated that in most cases this resolved within 48 to 72 hours with topical corticosteroid treatment.

#### Conclusions

The studies included in this Ophthalmic Technology Assessment evaluated the effect of LPI in PAC, and the outcomes assessed were change in angle width, effect on IOP control, disease progression, and complications after LPI. Of note, the level of evidence was fairly low. Most of the studies (53%, 19/36) were of level III evidence, and 28% (10/36) and 17% (6/36) of the studies were of level II and level I evidence, respectively. In addition, 81% of the studies (29/36) included Asian subjects only.

The available evidence indicates that LPI increases angle width as measured by gonioscopy, UBM, and ASOCT in eyes with and without PAS, based on level I evidence (for long-term change) and levels II and III evidence (for shortterm change). Up to one quarter of eyes without PAS (PACS subjects) may have gonioscopically defined persistent angle closure after LPI, representing nonpupillary block mechanisms of angle closure. Among all the studies reviewed in this Ophthalmic Technology Assessment, there was only 1 reported case of acute angle closure after LPI, 16 underscoring the rarity of this event after pupillary block has resolved. After an initial increase in angle width, there is a gradual narrowing of the angle with time, and this is attributed to lens changes. Of the several baseline parameters that were associated with persistent angle closure after LPI, most reflected a narrower angle at baseline or nonpupillary block mechanisms of angle closure, such as thicker iris, more anteriorly positioned ciliary body, and greater mean lens vault. Similar factors (narrow angle, thick lens, anteriorly positioned ciliary body) were also associated with persistence of positive response to provocative testing after LPI in the study by Sihota et al.<sup>33</sup>

After LPI, most PACS subjects can be expected to have no further treatment (level III). On the other hand, many PAC and APAC eyes, and most PACG eyes, are given additional treatment to control IOP. The limited data that we have suggest that LPI has a favorable effect on IOP, especially when extensive synechial closure or glaucomatous

damage has not occurred. For example, in 4 studies reviewed in this Ophthalmic Technology Assessment (level III), 19% and 44% of PAC eyes, <sup>24,25</sup> 13% of PACG eyes, <sup>25</sup> 21% of a mixed group of PAC and PACG eyes, <sup>32</sup> and 81% of APAC eyes<sup>29</sup> required no further treatment after LPI. Factors predictive for IOP elevation, or the need for further treatment after LPI, were those reflective of worse disease at baseline, such as higher IOP, greater cup-to-disc ratio, and greater synechial closure at presentation.

There were few studies that evaluated progression to glaucoma. In PACS and PAC, progression to glaucoma after LPI appears to be uncommon. In APAC, progression to PACG after LPI may be influenced by many variables, such as the presence or absence of glaucomatous optic neuropathy at the time of APAC, duration of symptoms before presentation for APAC, and cataract surgery after APAC. Disease progression in PACG was reported in only 2 studies, and the criteria used to define progression were not uniform. The factors associated with disease progression in these studies included the extent of angle closure, a family history of glaucoma, and duration of IOP elevation in APAC.

The issue of progression in PACS eyes is an important one; although the development of APAC or PACG in these eyes is not common, most are treated with LPI anyway because of the fear of APAC, a traumatic event that can be visually devastating. To better understand the role of LPI in PACS eyes, at least 3 prospective studies<sup>7,8,36</sup> have been conducted on PACS subjects who were treated unilaterally with LPI. However, to date, no data have been reported on disease progression in the treated versus untreated cohorts in these studies.

There were relatively few studies on complications after LPI, which included IOP spikes, dysphotopsia, anterior chamber bleeding, and cataract progression. Subjects included in 4 of 5 studies on IOP spikes after LPI were exclusively or predominantly PACS, but this complication is of higher concern in PACG eyes that are more vulnerable to IOP elevations. Although the issue of cataract progression remains of concern when considering prophylactic LPI in a population-based setting, it may be less relevant in the clinic-based setting, especially with the current trend toward early cataract or clear lens removal for angle closure.

In summary, LPI increases angle width in all stages of PAC and has a favorable effect on IOP in eyes without extensive angle or disc damage. Although there is a gradual decrease in angle width in PACS eyes after LPI, further treatment after LPI in this subgroup is infrequent. In contrast, additional treatment after LPI is more likely in PAC, APAC, and PACG eyes, and they should be monitored for IOP elevation and progression to glaucoma.

### **Future Research**

Important questions about LPI remain unanswered. Although progression to PACG is uncommon after LPI in PACS and PAC eyes, we do not know if the rate of incident PACG would have been higher if these patients had not had an LPI and were simply observed in the case of PACS, for example, or treated medically in the case of PAC with high

IOP. We also do not know the rate of incident APAC or PACG, nor can we predict which eye with PACS is likely to develop APAC or PACG so that prophylactic LPI can be better targeted. These questions are especially important when developing population-based strategies for the prevention of PACG, a disease that is projected to affect 21 million people worldwide by 2020. 43 For example, in 2001, Foster et al<sup>44</sup> estimated that the prevalence of "occludable angles" (defined as 270 degrees of ITC by gonioscopy) in the Chinese population was probably 28 million. To treat all of these cases with LPI in the hope of preventing progression to angle-closure disease would not only be a staggering undertaking but also would carry the potential to cause visual morbidity from complications of LPI such as cataract progression, which cannot be easily treated in many parts of the world.

The comparative efficacy of LPI versus other treatments for the various stages of PAC also needs further study. In APAC, LPI has been shown to be less effective than early phacoemulsification for the prevention of long-term IOP rise; however, the challenges of operating in this setting must be taken into account. One nonrandomized comparative study<sup>45</sup> of APAC eyes reported better IOP control with phacoemulsification performed 6 weeks after LPI versus LPI alone. The relative efficacy of these approaches requires further evaluation. Likewise, more data are needed to better define the role of LPI compared with other treatments for PAC and PACG. The traditional management algorithm of LPI, followed by medical therapy, followed by trabeculectomy, has been challenged by studies that support cataract surgery in lieu of trabeculectomy for medically controlled as well as uncontrolled PACG. 46,47 Traditional management has also been challenged by the EAGLE study,<sup>32</sup> which supports CLE instead of LPI as initial treatment for mild to moderate PACG and PAC with high IOP.

Finally, most studies on PAC have been on Asian subjects, and further research is required to determine if treatment outcomes after LPI would be different in other racial groups.

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Abbreviations and Acronyms:

AOD = angle opening distance; APAC = acute primary angle closure; ASOCT = anterior segment OCT; ATT = antithrombotic therapy; CLE = clear lens extraction; ECC = endothelial cell count; IOP = intraocular pressure; ITC = iridotrabecular contact; LPI = laser peripheral iridotomy; PAC = primary angle closure; PACG = primary angle-closure glaucoma; PACS = primary angle-closure suspect; PAS = peripheral anterior synechiae; PPP = Preferred Practice Pattern; RCT = randomized controlled trial; UBM = ultrasound biomicroscopy.

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