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中山大學
中山眼科中心
ZHONGSHAN OPHTHALMIC CENTER,
SUN YAT-SEN UNIVERSITY

Laser iridotomy in PACS
Zhongshan Angle-closure Prevention (ZAP) Trial

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Zhongshan Ophthalmic Center, Sun Yat-Sen University

Clinical Trial Registry: ISRCTN45213099

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Financial disclosure

- Software registration & IP ownership
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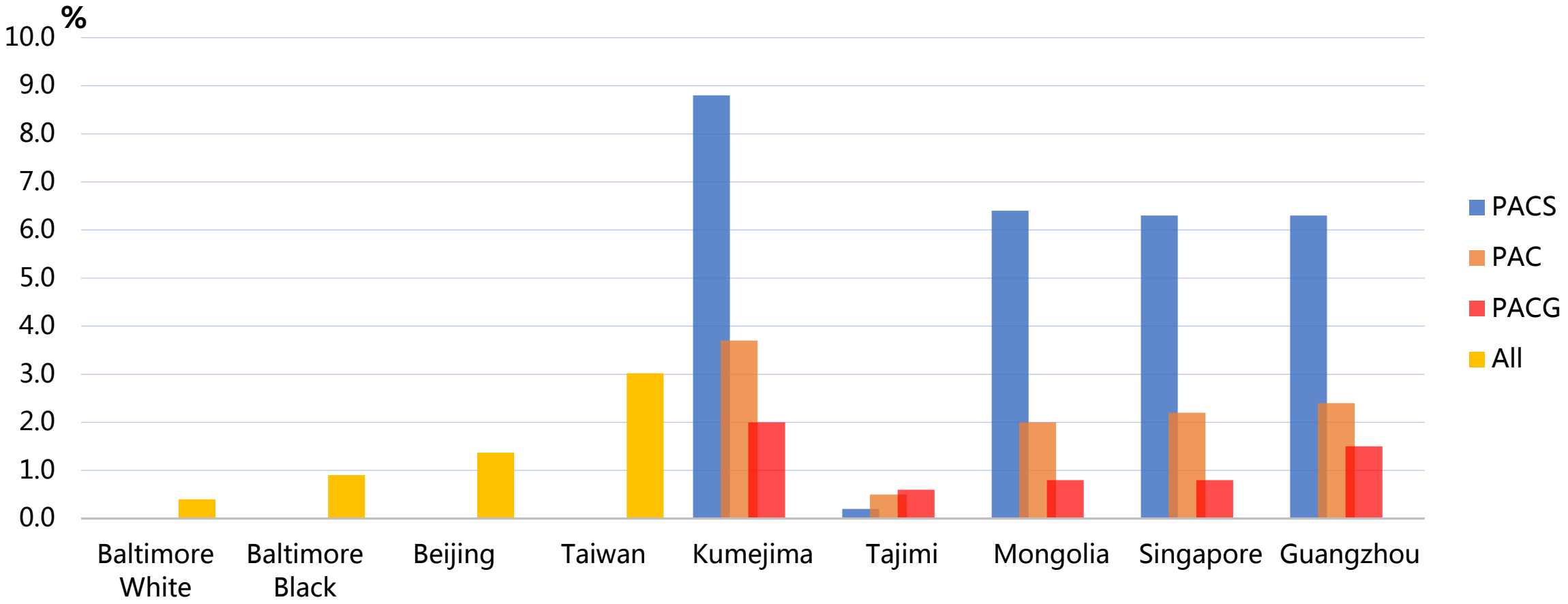
Prevalence of primary angle closure



Tielsch, Sommer, Katz, etc. *JAMA* 1991.

Buhrmann, Quigley, Barron,etc. *Invest Ophthalmol Vis Sci* 2000.

Bonomi, Marchini, Marraffa, etc. *Ophthalmol* 2000.

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Foster, Baasanhu, Alsbirk, etc. *Arch Ophthalmol* 1996. Foster, Oen, Machin, etc. JAMA *Ophthalmol* 2000.

He, Foster, Ge, etc. *Invest Ophthalmol Vis Sci* 2006.

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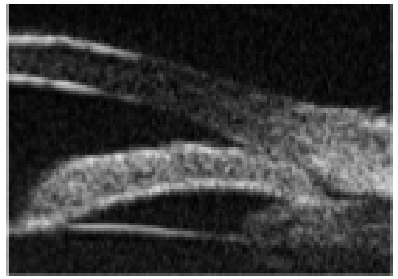
Hypothetical natural history of primary angle closure

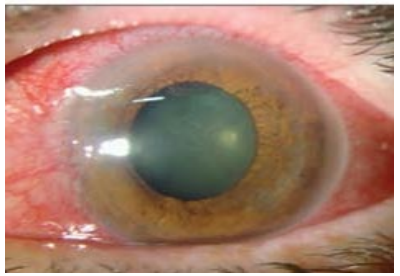
Primary Angle Closure Suspect(PACS)



Laser PI (prophylactic treatment)

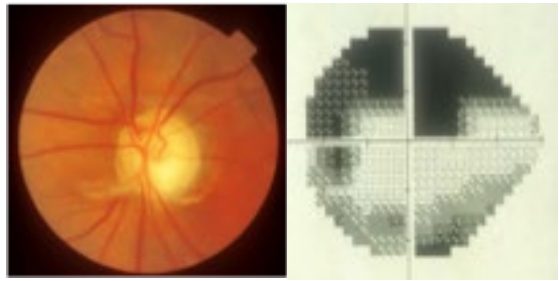
22% in 5 year

Primary Angle Closure (PAC)



28.5% in 5 year

Primary Angle Closure Glaucoma (PACG)



Foster, Paul J, et al. *Br J Ophthalmol* (2002)

Thomas. *Acta Ophthalmol* (2003)

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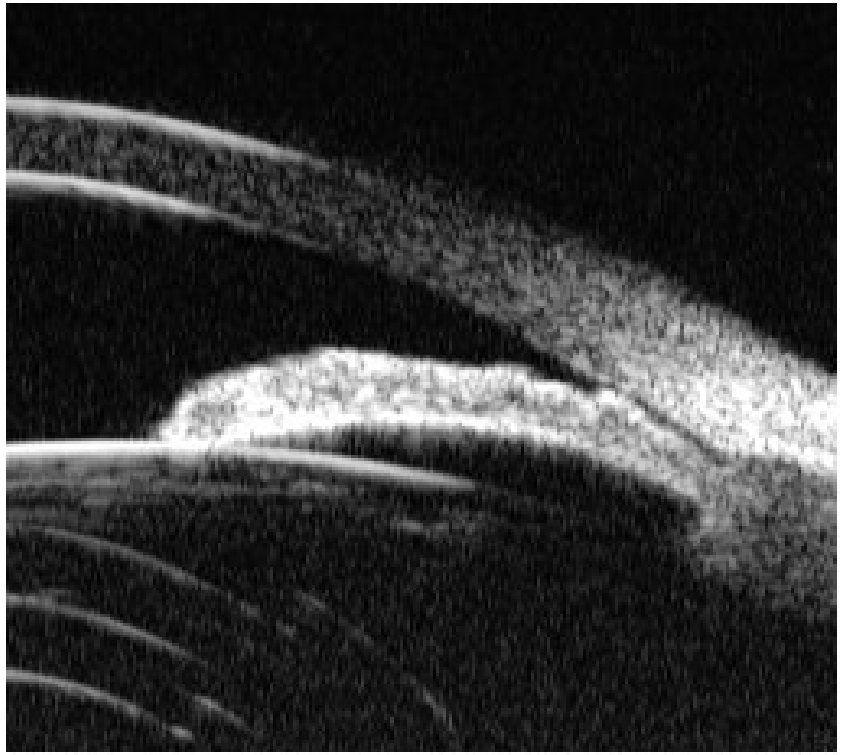
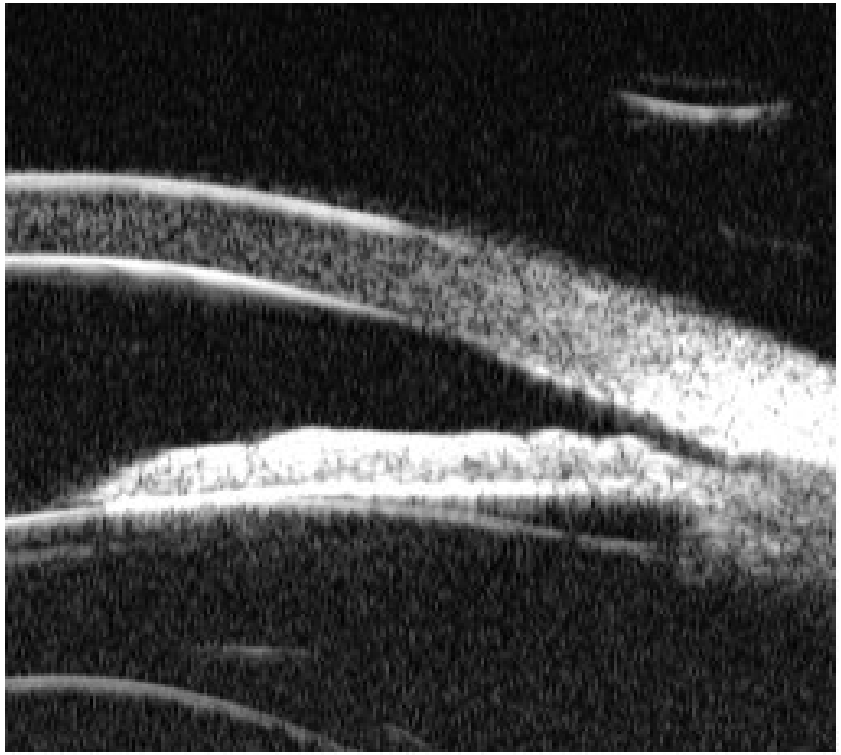
Short term angle width changes at 2-weeks after laser PI (among PACS enrolled in a population-based study)



Before PI



After PI

80% Open and 20% remained closed immediately after LPI

He et al. *Ophthalmology* 2007

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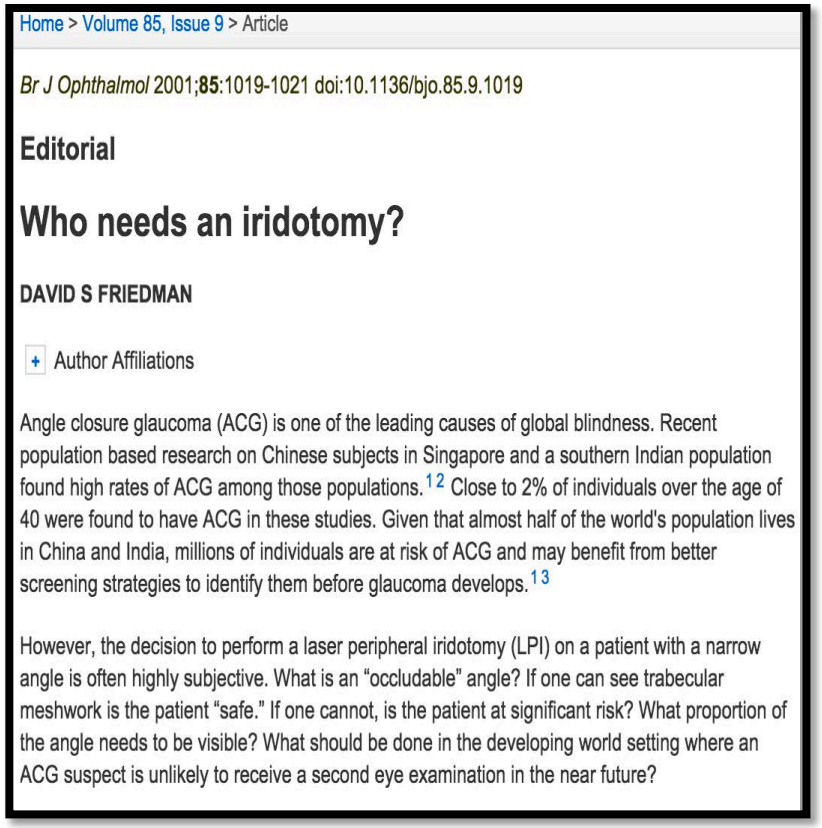
Who needs an iridotomy?
Require long-term randomized control trials



Home > Volume 85, Issue 9 > Article

Br J Ophthalmol 2001;**85**:1019-1021 doi:10.1136/bjo.85.9.1019

Editorial

Who needs an iridotomy?

DAVID S FRIEDMAN

+ Author Affiliations

Angle closure glaucoma (ACG) is one of the leading causes of global blindness. Recent population based research on Chinese subjects in Singapore and a southern Indian population found high rates of ACG among those populations.[1 2] Close to 2% of individuals over the age of 40 were found to have ACG in these studies. Given that almost half of the world's population lives in China and India, millions of individuals are at risk of ACG and may benefit from better screening strategies to identify them before glaucoma develops.[1 3]

However, the decision to perform a laser peripheral iridotomy (LPI) on a patient with a narrow angle is often highly subjective. What is an "occludable" angle? If one can see trabecular meshwork is the patient "safe." If one cannot, is the patient at significant risk? What proportion of the angle needs to be visible? What should be done in the developing world setting where an ACG suspect is unlikely to receive a second eye examination in the near future?

- China: 28 million PACS, 6-10% in Chinese
- USA: nearly 50,000 LPI annually
- UK: 10,284 in 2014-2015, many were PACS
- **Should we laser all of them?**
- What are the risk factors and who should receive prophylactic LPI?

Friedman DS. *Br J Ophthalmol* (2001)

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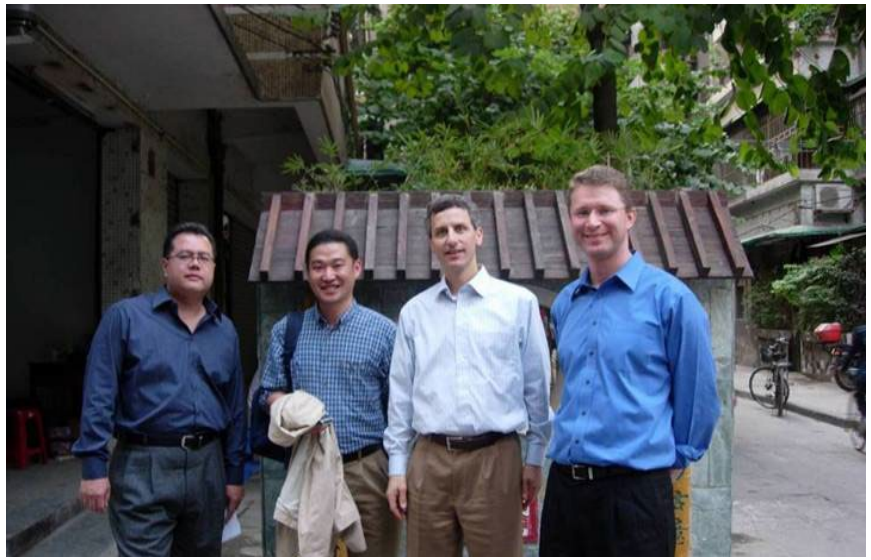
Zhongshan Angle-closure Prevention (ZAP) Trial



Tin Aung, Mingguang He, David Friedman, Paul Foster
(Liwan District, Guangzhou, 2006)

Specific objectives:

- Efficacy & safety of prophylactic LPI
- The natural history of PACS in untreated controls
- Predictors for PAC in untreated controls

6-years RCT to prove the efficacy and safety of prophylactic PI

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

Mingguang He, Yuzhen Jiang, Shengsong Huang, Dolly S Chang, Beatriz Munoz, Tin Aung, Paul J Foster, David S Friedman**

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.

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March 13, 2019
http://dx.doi.org/10.1016/S0140-6736(18)32607-2

See Online/Comment

The Lancet
published online first March 13, 2019

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Enrollment and Eligibility

Enrollment

- Aged 50-70 years
- Identified from a community-based screening program

Eligibility

- Bilateral primary angle closure suspects
- Static gonioscopy: posterior TM not visible in 180 degree of angle
- Without PAC or PACG

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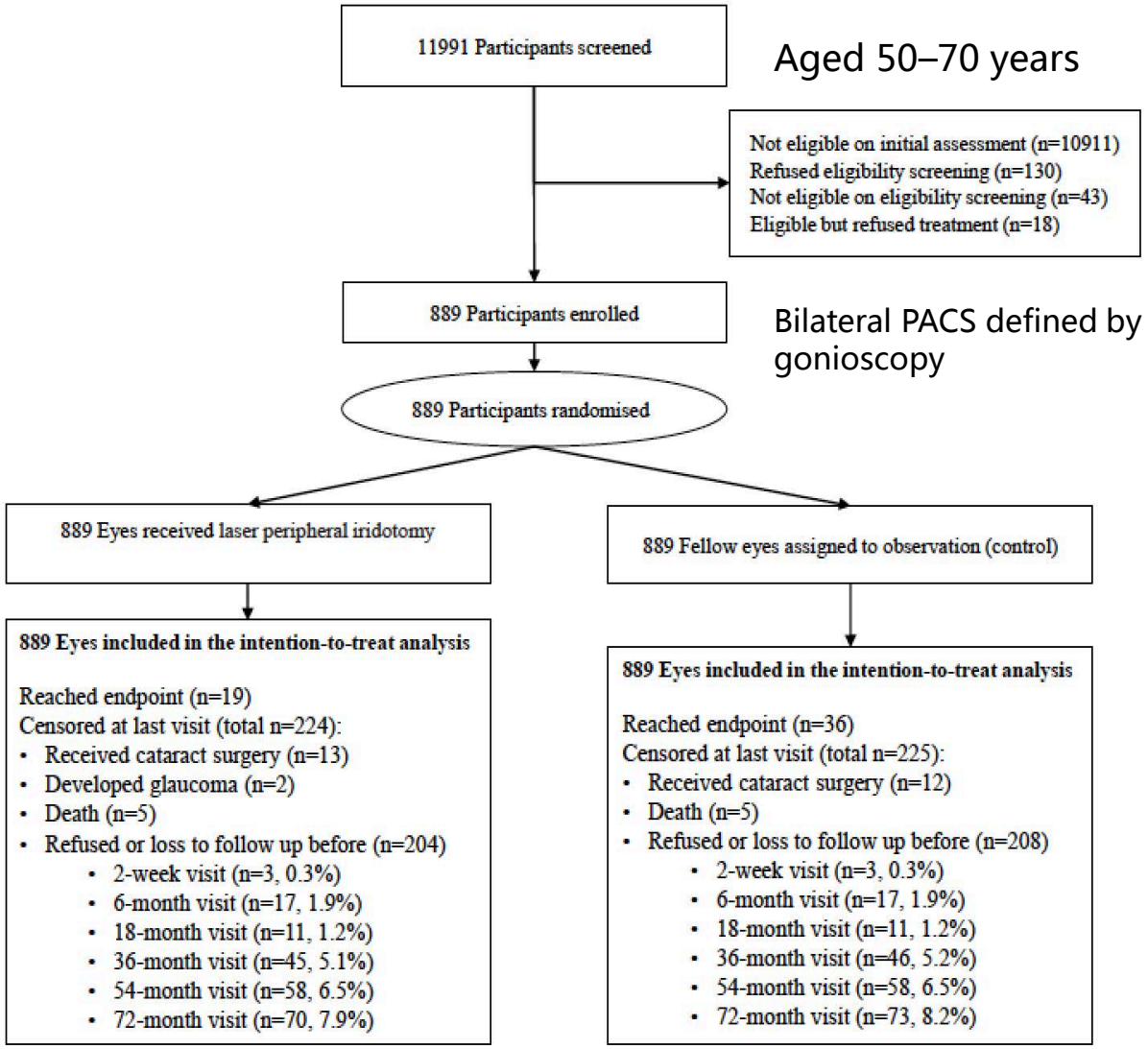
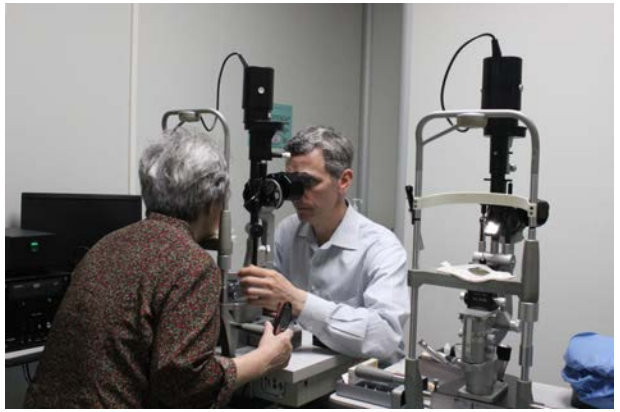
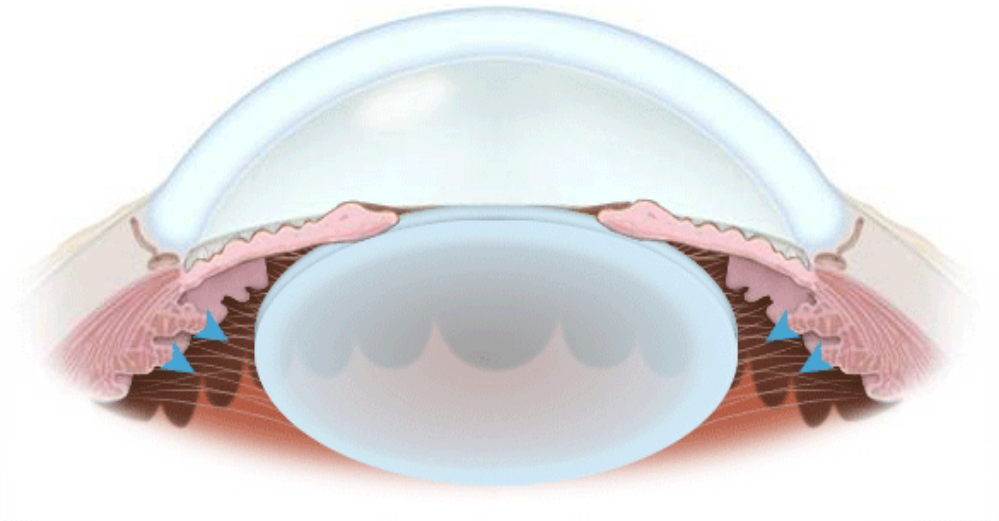


665 (75%) of 889 completed the 72 month study



Intervention: Single YAG laser



- YAG laser (Visulas YAG III)
- Initial setting of 1.5 mJ and titrating if needed
- Patent iridotomy of at least 200 µm in diameter
- Placed in a crypt or other thinnest
- Positioned beneath the superior lid

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Baseline

Characteristic	LPI (n=889)	Control (n=889)
Goldmann IOP, mmHg		
Before provocative test	14.3±2.6	14.3±2.6
After provocative test	18.6±3.2	18.6±3.2
Angle width on Gonioscopy		
Total angle width, score†	5.33±2.37	5.34±2.40
Number of closed quadrants, No. (%)		
2 quadrants	36 (4.05)	31 (3.49)
3 quadrants	114 (12.82)	113 (12.71)
4 quadrants	739 (83.13)	745 (83.8)

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Pair-wise analyses on primary endpoints at 72m visit

LPI / Control	No Endpoint	Endpoint	Total
No Endpoint	844	9 (1.0%)	853
Endpoint	26 (2.9%)	10	36 (4.0%)
Total	870	19 (2.1%)	889

McNemar's test: Statistic 8.26, P=0.0041

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Efficacy at 72 Month Follow-up
Survival analysis

Incident PAC - a composite endpoint of elevation of IOP, or PAS, or acute angle-closure

Primary analysis	LPI (889 eyes)	Non-LPI (889 eyes)	P-value
Endpoint Reached	19 (4.19/1000 eye-years)	36 (7.97/1000 eye-years)	**0.021**
IOP > 24mmHg	3 (0.66/1000 eye-years)	5 (1.11/1000 eye-years)	0.480
PAS ≥1 clock h	15 (3.31/1000 eye-years)	30 (6.64/1000 eye-years)	**0.024**
Acute attack	1 (0.22/1000 eye-years)	5 (1.11/1000 eye-years)	0.100

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How many PACS will be converted to PAC?

Incident PAC - a composite endpoint of elevation of IOP, or PAS, or acute angle-closure

Primary analysis	LPI (889 eyes)	Non-LPI (889 eyes)	P-value
Endpoint Reached	19 (4.19/1000 eye-years)	36 (7.97/1000 eye-years)	0.021
IOP > 24mmHg	3 (0.66/1000 eye-years)	5 (1.11/1000 eye-years)	0.480
PAS ≥1 clock h		30 (6.64/1000 eye-years)	
Acute attack	1 (0.22/1000 eye-years)	5 (1.11/1000 eye-years)	0.100

Among PACS identified from community screening
Incidence of PAC is very low
Majority of event are PAS formation
no immediate threat to vision

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How useful is prophylactic LPI?

Incident PAC - a composite endpoint of elevation of IOP, or PAS, or acute angle-closure

Primary analysis	LPI (889 eyes)	Non-LPI (889 eyes)	P-value
Endpoint Reached	19 (4.19/1000 eye-years)	36 (7.97/1000 eye-years)	0.021
IOP > 24mmHg	3 (0.66/1000 eye-years)	5 (1.11/1000 eye-years)	0.480
PAS ≥1 clock h	15 (3.31/1000 eye-years)	30 (6.64/1000 eye-years)	**0.024**
Acute attack	1 (0.22/1000 eye-years)	5 (1.11/1000 eye-years)	0.100

Risk on developing PAC was reduced by half
Statistically significant

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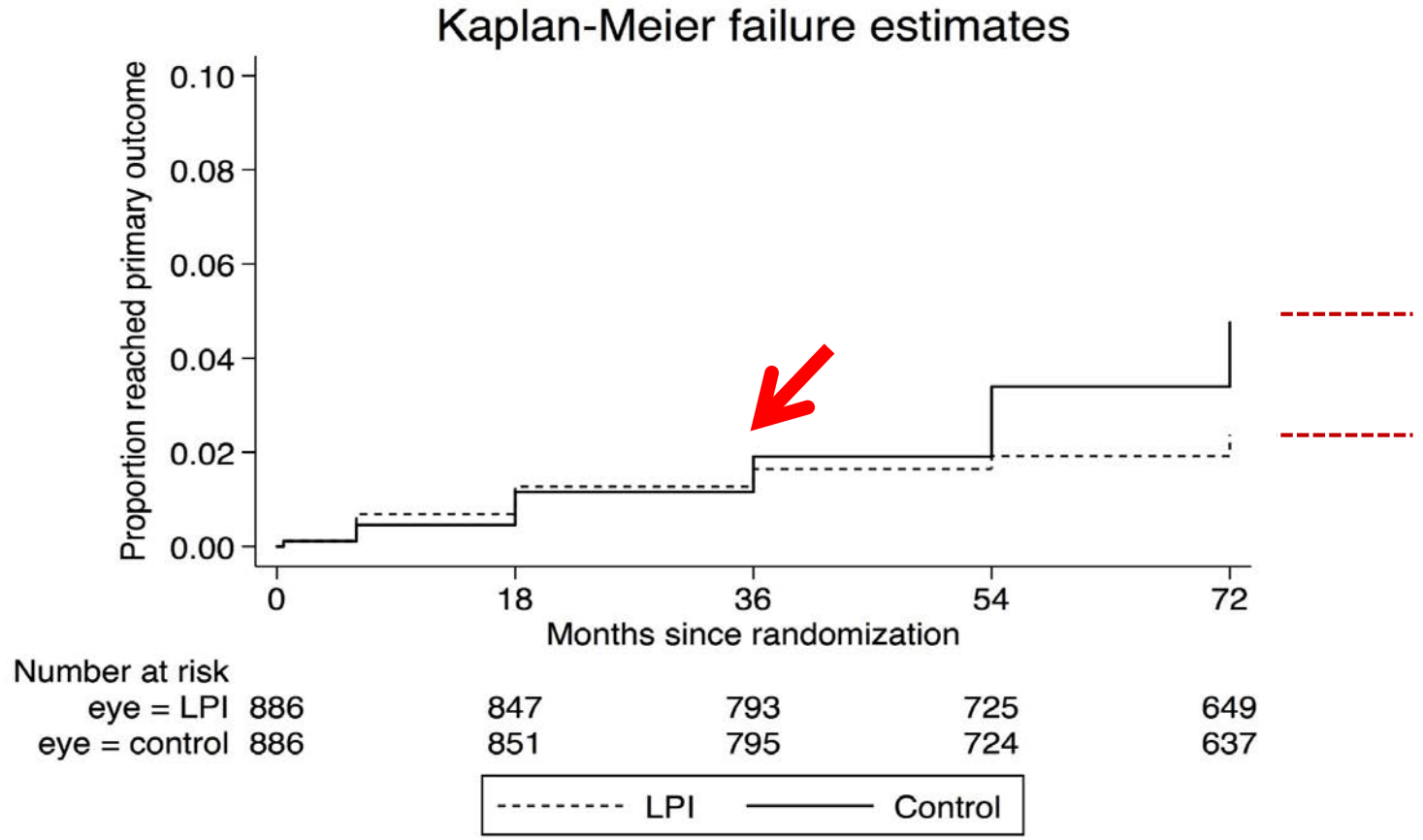
Cox proportional hazards model



LPI-treated eyes had a 47% reduction in the risk of reaching an endpoint

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When will the endpoints developed?
Primary endpoints = IOP elevation or PAS or acute attack

	LPI (n=889)	Control (n=889)	p-value
Reach primary endpoint (Total)	19 (4.19/1000EY)	36 (7.97/1000EY)	0.021
2 weeks	1 (0.1%)	1 (0.1%)	
6 months	5 (0.6%)	3 (0.3%)	
18 months	5 (0.6%)	6 (0.7%)	
36 months	3 (0.3%)	6 (0.7%)	
54 months	2 (0.2%)	11 (1.2%)	
72 months	3 (0.3%)	9 (1.0%)	

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When will the endpoints developed?
Endpoint = IOP elevation

	LPI (n=889)	Control (n=889)	p-value
IOP measures > 24 mmHg	3 (0.66/1000EY)	5 (1.11/1000EY)	0.480
2 weeks	0 (0.0%)	0 (0.0)	
6 months	1 (0.1%)	0 (0.0%)	
18 months	2 (0.2%)	2* (0.2%)	
36 months	0 (0.0%)	2* (0.1%)	
54 months	0 (0.0%)	0 (0.0%)	
72 months	0 (0.0%)	1* (0.1%)	

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When will the endpoints developed? Endpoint = PAS formation

	LPI (n=889)	Control (n=889)	p-value
PAS ≥1 clock hour	15 (3.31/1000EY)	30 (6.64/1000EY)	0.024
2 weeks	0 (0.0%)	0 (0.0%)	
6 months	4 (0.5%)	3 (0.3%)	
18 months	3 (0.3%)	5† (0.5%)	
36 months	3 (0.3%)	5† (0.5%)	
54 months	2 (0.2%)	11 (1.2%)	
72 months	3 (0.3%)	6† (0.7%)	

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When will the endpoints developed?
Endpoint = Acute attack

	LPI (n=889)	Control (n=889)	p-value
Acute attack	1 (0.22/1000EY)	5 (1.11/1000EY)	0.100
2 weeks	1§ (0.1%)	1§ (0.1%)	
6 months	0 (0.0%)	0 (0.0%)	
18 months	0 (0.0%)	0 (0.0%)	
36 months	0 (0.0%)	1‡ (0.1%)	
54 months	0 (0.0%)	0 (0.0%)	
72 months	0 (0.0%)	3 (0.3%)	

What does half risk reduction mean?
In the context of very low event rate

Overall annual risk reduction = 0.38%

Need to treat 44 to prevent 1 case of new PAC over 6 years

Assuming 35% PAC to PACG in next 5 years (R Thomas), Need to treat 126 to prevent 1 case of vision loss due to PACG over 10 years

Community-based screening to identify PACS and perform LPI

NOT recommended based on the low risk of progressing to PAC

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Who are likely to reach endpoints?

	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

- 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.

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What are long-term adverse effects of laser PI?

	LPI n=889	Control n=889
72-month:		
Change in endothelial cell density	-107.95±152.24	-93.20±134.23
Cataract LOCS III		
Nuclear opalescence	2.87±0.78	2.79±0.69
Nuclear color	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

Corneal endothelial loss & Cataract progression
No clinically significant difference observed

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Limitation

Observational bias

- Not able to mask examiners and patients

Misclassification risk

- Gonioscopy is partially subjective

Generalization

- Single center RCT
- Only directly applicable to Chinese PACS

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Take home messages

- Incidence of PAC/G among Chinese with PACS

  Very low

- Benefit of prophylactic LPI over 72 months

  Limited given the low event rate

- Widespread prophylactic LPI for PACS

  Not recommended

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Acknowledgements

Experts of trial steering committee (alphabetically)

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Advisory committee

- Prof Jian Ge, Dr Gus Gazzard (London, UK), Prof Dennis Lam (Hong Kong, China), Prof Jeffrey M Liebmann (New York, NY, US), Prof Robert Ritch (New York, NY, USA), Prof Xing-Huai Sun (Shanghai, China), Prof Clement Tham (Hong Kong, China), Prof Ningli Wang (Beijing, China), Dr Liang Xu (Nanjing, China), Prof Jia-Liang Zhao (Beijing, China)

Data monitoring and safety committee

- Dr Keith Barton (London, UK), Prof Don Budenz, (Chapel Hill, NC, USA), Dr Maureen McGuire, (Philadelphia, PA, USA), Prof Jim Tielsch (Chair, Baltimore, MD, USA)]

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ZAP angle closure prophylaxis Trial
Local research team in China
(Photo taken in 2008 when the study was initiated)

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