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REVIEW

Angle-closure glaucoma in East Asian and European people. Different diseases?

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Abstract

In contrast to the pattern of disease in Europeans, primary angle closure has a higher prevalence and tends to be asymptomatic in East Asians. The higher prevalence is attributed to differences in anterior chamber and angle anatomy. Several studies suggest that central anterior chamber depth is shallower in East Asians than in Europeans, although this is not universally accepted. It is debated whether pupil block is the predominant mechanism of angle closure in Asian people. Meaningful comparison between studies is currently hindered by differences in patient selection, examination technique, and case definition; however, the major scientific deficiency is the paucity of prospective followup data to give an insight into natural history of the disease. This review examines the data on prevalence, risk factors, and mechanism of angle closure. Special consideration is given to limitations of methodology in research to date, with the intention of developing more robust data in future studies.
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Keywords: primary angle-closure glaucoma; primary angle closure; anterior chamber; mechanism; pupil block; plateau iris configuration; iridotomy

Introduction

Several population-based studies have suggested that the prevalence of primary angle closure (PAC) is higher in East Asians than Europeans and Africans.[1,2] The majority of PAC in Asia tends to be chronic, asymptomatic disease.[3–7] The aetiology of PAC in East Asians, and particularly how anterior segment configuration influences mechanism of angle closure, is not fully understood. This article intends to review the available data and identify priority areas for future research. Particular consideration is given to the limitations of methodology in research to date, with the intention of developing more robust study protocols for future studies.

Definition and classification

Primary angle-closure glaucoma (PACG) has traditionally been divided into at least four clinical types: acute, subacute/intermittent, chronic and latent, based on the gonioscopic features of the drainage angle, intraocular pressure (IOP), and symptomatology.[8] However, symptoms appear not to be a good indicator of glaucomatous visual loss: 60–75% of persons suffering an acute episode of PAC recover without optic disc or visual field damage, at least in the short term.[9,10] The majority of Asian people suffering from angle-closure experience no symptoms.[3,4] This method of classification is increasingly being seen as inadequate for both clinical and research purposes.

There is a growing trend to adopt a uniform definition of glaucoma, synonymous with glaucomatous optic neuropathy (GON) resulting from different mechanisms of disease: open-angle, angle-closure, and secondary glaucoma. This was initially intended to standardize the use of the term 'glaucoma' in epidemiological research, as signifying visually significant disease. The use of this convention for angle-closure glaucoma has now been adopted by the American Academy of Ophthalmology[11] and SEAGIG (The Southeast Asia Glaucoma Interest Group).[12] Meaningful

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classification of the angle-closure process requires the use of two separate schemes in parallel (Table 1). Firstly, the stage of the angle-closure process should be identified. Three broad categories: suspect, established angle-closure and angle-closure glaucoma follow our conceptual model of the natural history, and reflect prognosis for vision.[13–15] Within each category, there is a spectrum of severity. Narrower angles are more likely to close than wider angles.[16] The likelihood of satisfactorily controlling IOP is inversely related to the circumference of trabecular meshwork affected by peripheral anterior synechiae (PAS).[17,18] Categorizing the stage of disease does not identify the mechanism causing the angle to close. Ritch's classification is currently the most logical for this purpose, dividing the mechanisms responsible for angle closure into four categories, each abnormality having a more posterior location, specifically: pupil block, plateau-iris, lens-induced, and retrolenticular causes.[19] Our preference is to substitute the term anterior, nonpupil block for plateau iris because we have found that, particularly among Asian people, some cases of angle closure remaining after PI (without posterior causes) do not display the characteristic angulation of the peripheral iris and apposition between apex of the ciliary body and posterior surface of the iris.

By using these the staging and mechanism schemes in parallel, management is guided by understanding why closure occurs, the site and severity of tissue damage, and the prognosis for vision. Table 2 compares the relative emphasis of the traditional and new, recommended methods of classifying angle closure.

Table 1 Parallel classification of stage and mechanism of primary angle closure

Disease staging

Stage 1: Narrow angle (angle-closure suspect)—an anatomical predisposition to closure.

Stage 2: Angle closure—Partial or total closure of the angle with synechiae and /or raised IOP (height and cumulative circumference of PAS should be recorded). (a) Non-ischaemic; (b) ischaemic—with tissue injury such as iris whorling or stromal atrophy, often history of symptoms.

Stage 3: Angle closure with glaucomatous optic neuropathy.

Mechanism of closure

A. Pupil block.

B. Anterior non-pupil block—including plateau iris and peripheral iris crowding.

C. Lens-related.

D. Factors behind the lens.

Table 2 Comparison of traditional *vs* combined staging and mechanism classification of angle-closure glaucoma

Classification	*Traditional scheme*	*Combined 'stage & mechanism' scheme*
Nosological basis	Symptoms	Site-specific tissue damage and dysfunction Presumed mechanism causing closure
Specifies visual dysfunction?	No	Yes
Indicates prognosis?	No	Yes
Guides targeted intervention?	No	Yes

Prevalence and incidence

Sparse data suggest that PAC and PACG are uncommon among European-derived people, with prevalence ranging from 0.04% in the Beaver Dam Study,[20] 0.06% in Melbourne,[21] 0.09% in Wales,[22] 0.4% in Baltimore (Oral communication, from JM Tielsch, PhD) to 0.6% in North Italy.[23] Again, the differences in diagnostic definition and insufficient power detecting the small prevalence make further comparison difficult.

Data detailing prevalence of PAC and PACG in Asia have increased considerably over the last decade. Table 3 compares studies of prevalence of PAC and PACG in Europeans and East Asians. Studies in Asia, in common with European studies, are of variable quality. Reports from a rural area near Beijing[1] and from Lhasa[24] both suffered methodological drawbacks; angle width was estimated by oblique flashlight test, gonioscopy was not performed for all subjects, and diagnostic criteria and methods were not clearly described. Another population study in Taiwan primarily aimed to evaluate screening techniques was compromised by a low participation rate.[4] A nationwide study of glaucoma prevalence in Japan suggested a much lower rate of PAC in Japanese, less than 1/3 of the rate seen in Chinese people.[25] In 1995, our group conducted a population-based study of glaucoma prevalence in Mongolia,[3] which found a rate of angle closure similar to Hu's survey in Beijing, although the diagnostic criteria differed considerably. In 1997–8, we also carried out a collaborative study of glaucoma prevalence in Chinese Singaporeans in the Tanjong Pagar district of the island.[26] When age- and gender-standardized, and with identical definitions, the prevalences of angle-closure suspects, angle closure, and PACG were almost identical to that seen in Mongolia.[13] These prevalence data are broadly consistent with the concept that angle closure is more common in Chinese people than in Europeans. One important issue identified in population surveys has been that only 25–40% of cases of angle-closure glaucoma cases have signs or a history of symptomatic attacks. This is important in interpreting the figures for incidence of 'acute' angle closure.[3–7]

Table 3 Comparison of the published prevalence data on primary angle closure glaucoma in different populations

Study location	*N⩾40 years (response)*	*Ratio: PACG : POAG*[a]	*Ratio: symptomatic : asymptomatic*	*Angle examination*[b]	*Diagnostic definition*[c]	*Prevalence*
Beijing (1989)[1]	3147 (96.0%)	43:1	34:9	Flashlight gonioscopy	Angle + IOP or symptoms	1.37%
Japan nationwide (1991)[20]	8126 (50.5%)	28:194 (including 150 NTG)	N/A	Gonioscopy for all	Angle + IOP	M: 50–69: 0.17% 70 + : 0.21% F: 50–69: 0.49% 70 + : 0.85%
Tibet (1992)[19]	1297 (92.4%)	N/A	N/A	Flashlight gonioscopy	Angle + IOP or symptoms	0.15% (two cases, all female)
Taiwan (1996)	562 (10.3%)	N/A	6:11	Gonioscopy for all	Angle + (IOP or DPPT or symptom)	3.02%
Mongolia (1996)[4]	942 (94.2%)	14:5	3:11	Gonioscopy for all	New ACS/PAC/PACG scheme	ACS: 6.4%[d] PAC: 2.0% PACG: 0.8%
Singapore (2000)[21]	1232 (71.8%)	14:22	6:8	Gonioscopy for all	New ACS/PAC/PACG scheme	ACS: 6.3% PAC: 2.2% PACG: 0.8%
Baltimore (1991)	5308		N/A	Not described	N/A	Black: 0.90% White: 0.40%
Italy (2000)[18]	4297 (73.9%)		N/A	Screening followed by gonioscopy	(Angle + symptoms + signs) + (IOP or disc or field)	M: 0.2% F: 0.9%

[a]The ratio shows the actual number of PACG or POAG cases identified.
[b]Angle closure was decided by either gonioscopy for all subjects or screening by oblique flashlight test firstly followed by gonioscopy for definitive diagnosis.
[c]Angle: anterior chamber angle; IOP: elevated intraocular pressure; Symptoms: previous confirmed symptoms of acute angle-closure; Signs: PAS or other signs of lens injury or ischaemic iris damage; DPPT: positive dark rooms prone provocative test; Disc: glaucomatous optic neuropathy; *Field*: glaucomatous visual field damage
[d]ACS: angle-closure suspect; PAC: primary angle closure; PACG: primary angle-closure glaucoma. The ACS category includes those in PAC and PACG, PAC category includes those in PACG.

Incidence data are useful in quantifying the amount of symptomatic, 'acute' angle closure. Age- and gender-standardized rates (/100 000/year in the population aged 30 years and older) for Finland, Croatia, Israel, Thailand, and Japan are 4.7, 5.6, 10.7, 7.0, and 11.4, respectively. These show a trend of increasing disease with more eastern location.[27,28] The Israeli data are not in keeping with this pattern, although without more information on the biometric characteristics of people from this region, it is difficult to proffer an explanation. Similarly, a study from Minnesota, USA, reported an incidence of 8.3 in the population aged 40 and older. The cases were 89% northern European, 8% Asian, and 3% black. Insufficient data are given to calculate a standardized rate.[29] None of these studies was prospective. Recently, there have been two studies in Singapore and Hong Kong that did prospectively study acute PAC in Chinese people, finding rates of 15.5 and 10.7.[27,30] Further research in Singapore used computerized hospital discharge data to compare the rate of angle closure in Chinese, Malay, and Indian people in Singapore. With figures of 12.2, 6.0, and 6.3, it seems that Chinese people suffer at least twice as much symptomatic angle closure as do Southeast Asian people (Thai, Malay, Indonesian, and others).[31] Chronic angle closure is currently not recognized as a common feature in European people, while among Asians it seems to be the predominant clinical manifestation. The implication of this is that the figures above for Asians probably represent only about a third of all angle closure. If we accept this, there does appear to be a considerable excess of angle closure in East Asians.

There have been few longitudinal studies of examining the rate of progression from angle-closure suspect status to established angle closure. One such study in Greenland found a 10-year incidence of angle closure in people with shallow anterior chambers of 16%.[32] Even higher rates have been reported in Southern India. Among the people with narrow drainage angles, 22% (95% CI: 9.8, 34.2) developed synechial (64%) or appositional angle closure (36%) over a period of 5 years.[15] The people with established angle-closure at the time of the initial survey were advised to undergo laser iridotomy. Eight of 28 people with angle closure re-examined (28%, 95% CI: 12, 45) had progressed to PACG over 5 years. One of nine who underwent LPI progressed compared to seven of 19 who refused LPI.[14] A randomized, controlled trial is currently underway to assess the benefits of prophylactic treatment for angle closure in Asian people.[33]

Anatomical and biometric risk factors

A small eye with a shallow anterior chamber, short axial length, small corneal diameter and steep curvature, shallow limbal chamber depth, and a thick relatively anteriorly positioned lens are all considered risk factors for PAC.[34–39] Anterior chamber depth (ACD) is widely regarded as the most easily measured index of risk of angle-closure. The majority of studies suggest an inverse relationship between prevalence of PAC and mean ACD in different populations.[37,40–43] However, a study comparing ACD in Taiwanese Chinese and both White and Black residents of Baltimore did not find a significant difference in the biometric characteristics of these three groups using handheld ultrasound. The authors suggested that factors other than ACD, such as high rates of plateau iris configuration, might explain the propensity to PAC in Chinese people.[44] This finding emphasizes that it is unlikely that a single risk factor will fully explain the inter-racial predisposition towards angle closure.

Gonioscopy

Gonioscopic examination remains the most important method of identifying signs of angle closure. Its successful usage is highly dependent on experience of the examiner. Several methods for grading the risk of angle closure have been devised. These include the Scheie, Shaffer, and Spaeth systems, which describe several characteristics of the drainage angle, including the proximity of the peripheral iris and trabecular meshwork on the basis of visibility of anatomical landmarks, or estimation of the angle width in degrees.[45–47] These gonioscopic grades provide an index of the likelihood of closure.[16] A dichotomous classification of drainage angle width (and perceived risk of closure) is used in epidemiological research. Angles have been termed 'occludable' or 'not occludable' based on the visibility of the posterior trabecular meshwork in the static gonioscopy. It is likely that the criteria used to make this distinction are unduly stringent, and exclude many cases of angle closure. Attempts have been made to remove some of the subjectivity from gonioscopy. The use of a graticule in the slit lamp eyepiece to measure the distance from iris insertion to Schwalbe's line, termed 'biometry gonioscopy,' has been suggested as a simple, accurate, and more reproducible method of gonioscopic examination.[48] Dynamic or indentation gonioscopy remains indispensable in differentiating synechial from appositional angle closure.

Comparing several studies, racial differences in gonioscopic findings are apparent. The percentages of eyes with Shaffer grade $\leqslant 2$ angle width was as low as 3.8% in the Framingham study (European people)[49] and as high as 47.8% (8.5% for grade 0 or 1) in Vietnamese clinic patients in the USA in the same age group.[50] Shaffer grade 1 angles were present in 9% Cape-Malay

people in South Africa (of mixed African and Southeast Asian ancestry).[51] Using identical definitions of an 'occludable' angle, our work in Mongolia and Singapore found occludable angles in 6.4 and 6.3%, respectively.[52]

A hospital-based study comparing angle configuration in healthy East Asians, Afro-American, and Caucasians in the US, using the Spaeth gonioscopic grading scheme, gives another perspective.[53] Iris insertion was found to be more anterior in Asian Americans compared with white and black subjects, although the recruited Asian individuals tended to be younger and more myopic. This characteristic was assumed to increase the risk of PAS formation in Asian eyes. In contrast, the results of a study using biometric gonioscopy found no significant difference in the mean exposed trabecular width between Singaporean Chinese, white, and black people in Baltimore after matching the age and sex. The Chinese people did, however, have deeper angles when young and significantly shallower angles in older age compared with black and white people, resulting in similar mean angle widths. There is growing evidence that Chinese populations in industrialized countries may be undergoing a pronounced change in ocular biometric characteristics, associated with higher rates of myopia in younger people,[54,55] emphasizing that caution is required when drawing inferences regarding longitudinal trends from cross-sectional data.

Mechanism of angle closure

Pupil block is believed to be the major causative mechanism in most cases of angle closure in the West. Chandler[56] and Lowe[57] suggested that pupil block is the consequence of contact between iris and anterior lens surface of the lens. In 1964, Lowe proposed a more sophisticated model of pupil block, describing a conceptual force vector onto the lens surface from resulting from co-contraction of both sphincter and dilator muscles.[58] Using pharmacological provocation tests and anterior segment photographs, Mapstone refined this vector model of pupil-blocking force, proposing that it resulted from three forces—sphincter and dilator muscles, as well as iris elasticity, causing relative or absolute obstruction to aqueous flow.[59] In eyes with PAC, the unique anatomical configuration (anterior location of the lens causing a shallow anterior chamber) decreases the angle between the respective vectors, increasing the resultant force onto the lens surface, and exacerbating relative pupil block. The pupil-blocking force then precipitates a resistance to aqueous flow from the posterior to anterior chamber. This then generates a pressure gradient across the iris, leading to anterior bowing.

However, the variable efficacy of iridotomy and the advent of UBM imaging have led to the realization that the pupil block hypothesis does not satisfactorily explain many cases of angle closure. The term 'plateau iris' is often (we believe incorrectly) used as an umbrella term for nonpupil-block angle closure. It is a term that describes both a particular configuration of the peripheral iris, and a clinical syndrome characterized by angle closure occurring in an eye with a patent iridotomy and plateau iris configuration. In European people, this configuration is usually caused by anteriorly rotated ciliary processes that push the peripheral iris forward, resulting in the characteristic angulation. The gonioscopic features of plateau iris were firstly described by Wand,[60] with the underlying anatomical cause demonstrated by UBM imaging.[61,62] Iridotomy alone is often ineffective in preventing angle closure in 'pure' plateau iris. The risk of closure depends on the height of the plateau and the width of the 'gutter' between the peripheral iris and trabecular meshwork (Figures 1a and b).

'Prominent last iris roll' is a term, sometimes attributed to Fuchs, used to describe an anterior, nonpupil-block entity. Eyes with this condition have a very thick iris which is peripherally thrown into prominent circumferential folds (Figure 1c), occupying a larger proportion of anterior chamber volume than a thin, blue iris. With dilation of the pupil, these folds become even more pronounced, and may come into contact with the trabecular meshwork. A recent review suggested that only 38% of angle closure in Chinese people is attributable solely to pupil block. Around 8% of cases are caused by nonpupil-block mechanisms alone, with the remaining 54% resulting from a combination of the two processes.[63] Hung reported that the dark-prone provocation test was 60% positive (arise of 8 mm Hg or more) in 60% of Chinese eyes post-iridectomy, compared with 12.5% in normal eye.[64] All were at a relatively early stage of synechial closure (eyes with more than 120° of PAS were excluded). Such descriptions highlight the complexity of many cases of angle closure, where it is rare for one mechanism to solely responsible for closure.

External factors often seem to precipitate symptomatic angle closure. There appears to be a consistent association between angle closure and climatic conditions, although the precise conditions in which attacks occur vary. The general trend appears to be that extremes of temperature, possibly causing the population to remain indoors, may be the link.[27,65–69] Anticholinergic agents benzhexol[70] and ipratropium bromide[71,72] are recognized as precipitating angle closure. Upper respirator tract infections and cold remedies may have the same effect.[30,73] Posterior segment pathological processes[74] or therapeutic procedures[75] occasionally cause a rise in IOP associated with transient angle

closure. Idiosyncratic reactions to sulphonamide agents causing transient myopia, choroidal detachments, and profound shallowing of the anterior chamber are well recognized as inducing 'acute' angle closure.[76–78] This last observation has prompted Quigley to suggest a choroidal vascular mechanism in some cases of PAC.[79] However, despite the increasing sophistication of our theoretical models of angle closure, we still do not fully understand the reason for closure in many cases.

Figure 1 These ultrasound biomicrographs illustrate cases of angle closure without convexity of the posterior surface of the iris that accompanies pupil block. Note that the posterior surface of the iris is flat where not in contact with the ciliary body, suggesting the absence of a pressure gradient across the iris. Although considerable overlap exists, conceptually there are three distinct groups in Chinese eyes. (a) Shows typical plateau iris configuration with a pronounced angulation in the peripheral third of the iris caused by an anteriorly rotated ciliary body distorting the peripheral iris. (b) Has a bulky peripheral iris which angulates sharply to insert into the middle of the anterior surface of the ciliary body. There is no support from the apex of the ciliary body. (c) Has a similarly bulky peripheral iris. There is contact between the posterior surface of the iris and the ciliary body, although the apparent angulation is attributable to a prominent last iris roll. The iris inserts into the basal aspect of the anterior ciliary body.

Effect of PI

Laser iridotomy remains the cornerstone of management of angle closure, and results in a dramatic change in iris profile in cases with a pure pupil-block mechanism (Figures 2a and b). It results in a significant increase in angle width in both Europeans and Asians with narrow angles.[80,81] One study of predominantly Chinese people with narrow drainage angles found that PI produced a significant increase in angle width. It was also noted that the changes in iris morphology following PI were different occurring between normal and reduced illumination, suggesting an additional mechanism responsible for angle occlusion in the dark, independent of pupil block.[81] The efficacy of PI for disease control is dependent both on the underlying mechanism causing closure, and the stage of the disease. Among people of African and Asian descent, greater extent of PAS, a higher presenting IOP, and a larger cup:disc ratio are all predictors of poor pressure control following iridotomy.[17,18] Following an episode of symptomatic angle closure, reports suggest that satisfactory IOP control can be achieved in 42–72% of cases with PI alone.[82,83] Once GON, defined as structural damage to the disc and a field defect, have developed, virtually all cases (94–100%) will require further treatment to control IOP.[84] Inferring that earlier intervention will definitely lead to a beneficial outcome in the long term is hindered by the phenomenon of 'lead-time bias'—the concept that earlier detection and treatment merely increase the

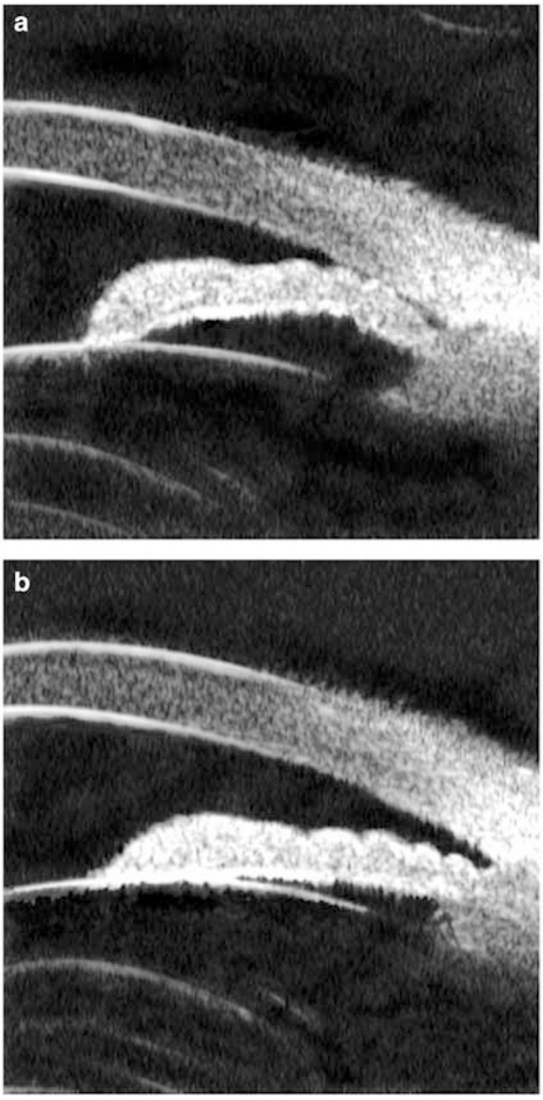

Figure 2 (a) and (b) are ultrasound biomicrographs illustrating the effect of peripheral laser iridotomy on pupil block. (a) Shows a pronounced angulation of the midperipheral iris and appositional contact around the level of Schwalbe's line. Note the aqueous-filled space (Mapstone's sinus) posterior to the area of contact between iris and trabecular meshwork. Such eyes may have apparently extensive closure, but normal or only mildly elevated IOP, as the bulk of the trabecular meshwork remains nonoccluded in the early stages of primary angle closure. Gonioscopic inspection of the iris configuration may suggest plateau iris. (b) Shows the same segment of the same eye following laser iridotomy. The angulation of the posterior surface of the mid-peripheral iris present in (a) without support from the ciliary body has completely resolved. This highlights the importance of laser iridotomy as the first step in management primary angle closure. The benefits can be difficult to predict, and in some cases are very pronounced.

period of followup, until the time when control of the disease is lost, with no change in outcome for the individual. However, the efficacy of prophylactic iridotomy or iridectomy in the fellow eye of one who has suffered 'acute' angle closure, in both Europeans and Asians (89–100% control of IOP),[33,82,85] is a persuasive argument that iridotomy, performed at an early stage in the disease process, does indeed have a beneficial effect.

Despite considerable research effort in the field of angle closure over the last decade, we still have many unanswered questions about the natural history and pathogenesis of the disease. The process of PAS formation is poorly understood. Similarly, we do not understand how, or indeed whether, appositional closure prior to formation of PAS affects trabecular meshwork function. The optimal management following PI remains to be investigated in an organized fashion, although paracentesis, lens extraction, and particularly iridoplasty may offer significant benefits over our previous management strategies.[86–89] In future treatment trials and the search for the definitive mechanism(s) of angle closure, the use of updated classification and outcome measures will almost certainly help. UBM and Scheimpflug image analysis have been major advances, permitting quantitative analysis of anterior segment anatomy. Anterior segment optical coherence tomography promises even greater biometric accuracy.

In summary, there are similarities in the characteristics of angle closure between Asians and Europeans. ACD appears to be a significant risk factor in both, and when there is advanced closure with GON, laser iridotomy alone will not control the disease. An important difference is that, among Asian people, the disease is typically asymptomatic. In addition, there is an increasing opinion that nonpupil-block mechanisms may account for a significant proportion of angle closure in Southern China. In view of our previous estimates that 1.7 million people in China are blind in both eyes from glaucoma, 91% due to angle closure,[89] there is a pressing need for data addressing the feasibility of screening for angle closure, and the benefit of prophylactic laser iridotomy in China.

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