

## Review

# The Pathophysiology and Treatment of Glaucoma

## A Review

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**IMPORTANCE** Glaucoma is a worldwide leading cause of irreversible vision loss. Because it may be asymptomatic until a relatively late stage, diagnosis is frequently delayed. A general understanding of the disease pathophysiology, diagnosis, and treatment may assist primary care physicians in referring high-risk patients for comprehensive ophthalmologic examination and in more actively participating in the care of patients affected by this condition.


**OBJECTIVE** To describe current evidence regarding the pathophysiology and treatment of open-angle glaucoma and angle-closure glaucoma.


**EVIDENCE REVIEW** A literature search was conducted using MEDLINE, the Cochrane Library, and manuscript references for studies published in English between January 2000 and September 2013 on the topics open-angle glaucoma and angle-closure glaucoma. From the 4334 abstracts screened, 210 articles were selected that contained information on pathophysiology and treatment with relevance to primary care physicians.

**FINDINGS** The glaucomas are a group of progressive optic neuropathies characterized by degeneration of retinal ganglion cells and resulting changes in the optic nerve head. Loss of ganglion cells is related to the level of intraocular pressure, but other factors may also play a role. Reduction of intraocular pressure is the only proven method to treat the disease. Although treatment is usually initiated with ocular hypotensive drops, laser trabeculoplasty and surgery may also be used to slow disease progression.

**CONCLUSIONS AND RELEVANCE** Primary care physicians can play an important role in the diagnosis of glaucoma by referring patients with positive family history or with suspicious optic nerve head findings for complete ophthalmologic examination. They can improve treatment outcomes by reinforcing the importance of medication adherence and persistence and by recognizing adverse reactions from glaucoma medications and surgeries.

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**T**he glaucomas are a group of optic neuropathies characterized by progressive degeneration of retinal ganglion cells. These are central nervous system neurons that have their cell bodies in the inner retina and axons in the optic nerve. Degeneration of these nerves results in *cupping*, a characteristic appearance of the optic disc and visual loss.<sup>1</sup> The biological basis of glaucoma is poorly understood and the factors contributing to its progression have not been fully characterized.<sup>2</sup>

Glaucoma affects more than 70 million people worldwide with approximately 10% being bilaterally blind,<sup>3</sup> making it the leading cause of irreversible blindness in the world. Glaucoma can remain asymptomatic until it is severe, resulting in a high likelihood that the number of affected individuals is much higher than the number known to have it.<sup>4,5</sup> Population-level surveys suggest that only 10% to 50% of people with glaucoma are aware they have it.<sup>4-8</sup> Glaucomas can be classified into 2 broad categories: open-angle glaucoma and angle-closure glaucoma. In the United States, more than 80% of

cases are open-angle glaucoma; however, angle-closure glaucoma is responsible for a disproportionate number of patients with severe vision loss.<sup>9,10</sup> Both open-angle and angle-closure glaucoma can be primary diseases. Secondary glaucoma can result from trauma, certain medications such as corticosteroids, inflammation, tumor, or conditions such as pigment dispersion or pseudo-exfoliation.

A recent *JAMA* Rational Clinical Examination systematic review of primary open-angle glaucoma diagnosis found that the risk of glaucoma was highest when examination revealed an increased cup-disk ratio (CDR), CDR asymmetry, disc hemorrhage, or elevated intraocular pressure.<sup>11</sup> Primary open-angle glaucoma was also more likely when there was a family history of the disease, black race, or advanced age (Box). The primary care physician also should be aware of the risk of developing glaucoma in patients being treated with systemic or topical corticosteroids.<sup>12</sup> Patients at risk should be referred to an eye care practitioner. This review explores pathophysiology of the disease and its treatment.

## Methods

A literature search was conducted using MEDLINE, the Cochrane Library, and manuscript references for studies published in English between January 2000 and September 2013 on the topics open-angle and angle-closure glaucoma. From the 4334 abstracts screened, 210 articles were selected that contained information on pathophysiology and treatment with relevance to primary care physicians.

### Primary Open-Angle Glaucoma

#### Pathophysiology

Although the pathogenesis of glaucoma is not fully understood, the level of intraocular pressure is related to retinal ganglion cell death. The balance between secretion of aqueous humor by the ciliary body and its drainage through 2 independent pathways—the trabecular meshwork and uveoscleral outflow pathway—determines the intraocular pressure. In patients with open-angle glaucoma, there is increased resistance to aqueous outflow through the trabecular meshwork. In contrast, the access to the drainage pathways is obstructed typically by the iris in patients with angle-closure glaucoma (Figure 1).

Intraocular pressure can cause mechanical stress and strain on the posterior structures of the eye, notably the lamina cribrosa and adjacent tissues (Figure 2).<sup>13</sup> The sclera is perforated at the lamina where the optic nerve fibers (retinal ganglion cell axons) exit the eye. The lamina is the weakest point in the wall of the pressurized eye. Intraocular pressure-induced stress and strain may result in compression, deformation, and remodeling of the lamina cribrosa with consequent mechanical axonal damage and disruption of axonal transport<sup>14,15</sup> that interrupts retrograde delivery of essential trophic factors to retinal ganglion cells from their brainstem target (relay neurons of the lateral geniculate nucleus). Studies involving cats and monkeys with experimentally induced ocular hypertension have demonstrated blockade of both orthograde and retrograde axonal transport at the level of the lamina cribrosa.<sup>16</sup> Disrupted axonal transport occurs early in the pathogenesis of glaucoma in experimental systems resulting in collections of vesicles and disorganization of microtubules and neurofilaments in the prelaminar and postlaminar regions. Similar ultrastructural changes in optic nerve fibers are seen in postmortem human eyes that have glaucoma.<sup>13</sup> Because there also may be mitochondrial dysfunction in retinal ganglion cells and astrocytes,<sup>17</sup> high levels of energy demand may be difficult to meet during periods of intraocular pressure-induced metabolic stress.

Glaucomatous optic neuropathy can occur in individuals with intraocular pressures within the normal range. In such patients, there may be an abnormally low cerebrospinal fluid pressure in the optic nerve subarachnoid space resulting in a large pressure gradient across the lamina.<sup>18,19</sup> Impaired microcirculation, altered immunity, excitotoxicity, and oxidative stress may also cause glaucoma. Primary neural pathological processes may cause secondary neurodegeneration of other retinal neurons and cells in the central visual pathway by altering their environment and increasing susceptibility to damage.<sup>20</sup>

#### Genetics

Several genes—including myocilin (*MYOC*, *GLCIA*) (CCDS1297.1),<sup>21</sup> optineurin (*OPTN*, *GLCIE*) (CCDS7094.1),<sup>22</sup> and WD repeat

#### Box 1. Risk Factors That Should Prompt Referral to an Eye Care Practitioner for Evaluation for Glaucoma

- Older age
- Family history of glaucoma
- Black race
- Use of systemic or topical corticosteroids
- High intraocular pressure

domain 36 (*GLCTG*) (CCDS4102.1)<sup>23</sup>—are associated with a monogenic, autosomal dominant trait; however, these genes account for less than 10% of all glaucoma cases.<sup>24</sup> The first reported locus for primary open-angle glaucoma was located on chromosome 1 (*GLCIA*). The relevant gene at the *GLCIA* locus is *MYOC*, which encodes the protein myocilin. Disease-associated mutations of myocilin generally occur in the juvenile or early adult form of primary open-angle glaucoma, usually characterized by very high levels of intraocular pressure. In populations of adults with primary open-angle glaucoma, the prevalence of myocilin mutations varies from 3% to 5%.<sup>24</sup> Carriers of disease-associated mutations develop the glaucoma phenotype in an estimated 90% of the cases.<sup>24</sup> The mechanism of myocilin-related glaucoma has not been fully elucidated.<sup>24</sup> It appears that mutations alter the myocilin protein in a way that disrupts normal regulation of intraocular pressure. Disease-associated forms of myocilin interfere with protein trafficking and result in intracellular accumulation of misfolded protein. Failure to adequately secrete the protein is thought to somehow cause the intraocular pressure to increase.

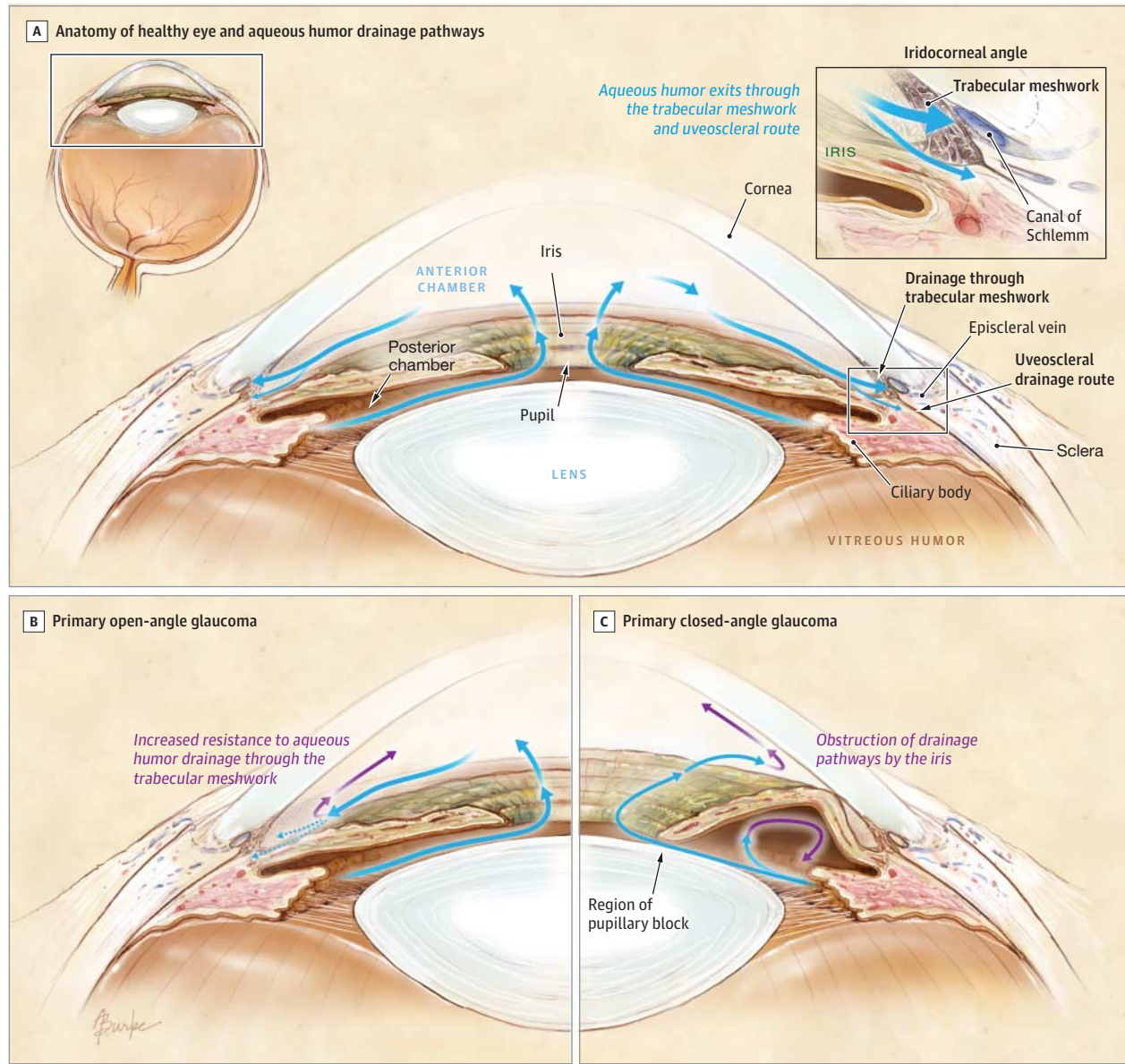
In contrast to individuals with the *MYOC* gene, those with the *OPTN* gene have normal levels of intraocular pressure.<sup>22</sup> Although the mechanism relating the *OPTN* gene variants to glaucoma have not been elucidated, there is evidence suggesting that optineurin may have a neuroprotective role by reducing the susceptibility of retinal ganglion cells to apoptotic stimuli.

A growing number of studies use genome-wide scans to look for glaucoma susceptibility loci. The *CAVI/CAV2* (HGNC:1527/HGNC:1528) locus on 7q34 may be associated with primary open-angle glaucoma in European-derived populations. This finding has been replicated by independent studies.<sup>25</sup> These genes encode proteins (caveolins) involved in the generation and function of caveola, which are invaginations of the cell membrane involved in cell signaling and endocytosis. The *CDKN2BAS* (HGNC:34341) locus on 9p21 was shown to be related to glaucoma risk in multiple cohorts.<sup>26</sup> The mechanism by which these genes might contribute to primary open-angle glaucoma is not clear, but they may interact with transforming growth factor  $\beta$ , a molecule regulating cell growth and survival throughout the body. Despite promising results, susceptibility genes that have been identified to date for primary open-angle glaucoma only have a modest effect size in explaining glaucoma risk.

#### Clinical Presentation and Diagnosis

Although elevated intraocular pressure is a very consistent risk factor for the presence of glaucoma, several population-based studies found intraocular pressure was lower than 22 mm Hg in 25% to 50% of individuals with glaucoma.<sup>1,14</sup> Despite the strong association between elevated intraocular pressure and glaucoma, substantial numbers of people with elevated intraocular pressure never develop glau-

Figure 1. Aqueous Humor Drainage Pathways of Healthy and Glaucomatous Eyes



coma even during lengthy follow-up.<sup>1</sup> Glaucoma progresses without causing symptoms until the disease is advanced with substantial amounts of neural damage. When symptoms do occur, the disease results in vision loss with concomitant reduction in quality of life and the ability to perform daily activities, such as driving. Early intervention is essential to slow the progression of the disease. Referral to an eye care practitioner should occur for patients at risk of glaucoma (Box 1).

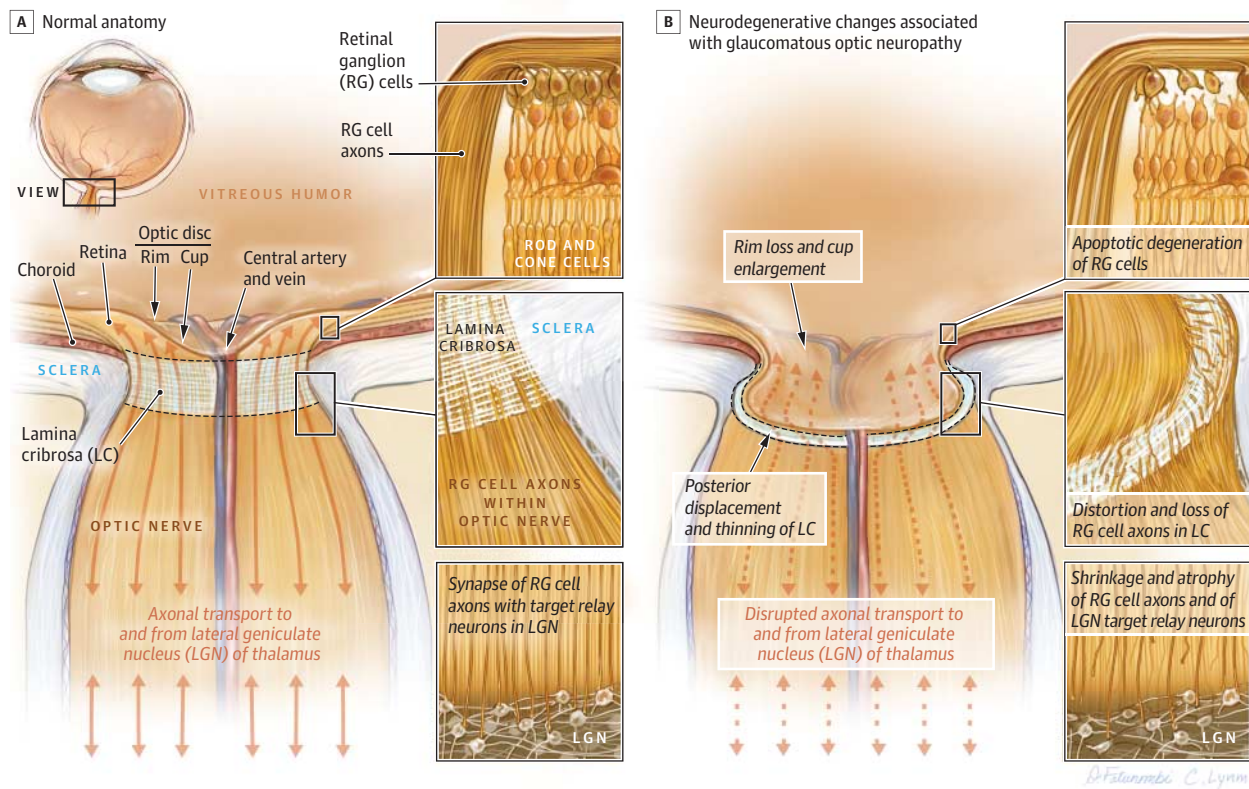
With retinal ganglion cell death and optic nerve fiber loss in glaucoma, characteristic changes in the appearance of the optic nerve head and retinal nerve fiber layer occur.<sup>1</sup> These changes are the most important aspect of a glaucoma diagnosis and can be identified during ophthalmoscopic examination of the optic nerve head (Figure 3). The importance of conducting an appropriate ophthalmologic examination of the eye cannot be overstated with respect to early detection of glaucoma. Retinal ganglion cell loss causes progressive de-

terioration of visual fields, which usually begins in the midperiphery and may progress in a centripetal manner until there remains only a central or peripheral island of vision.

Because there is no single perfect reference standard for establishing the diagnosis of glaucoma, early diagnosis can be challenging. Although examination of the optic nerve head can reveal signs of neuronal loss, wide variability of its appearance in the healthy population makes identification of early damage challenging. Presence of characteristic visual field defects can confirm the diagnosis, but as many as 30% to 50% of retinal ganglion cells may be lost before defects are detectable by standard visual field testing.<sup>13,27</sup> Longitudinal evaluation and documentation of structural damage to the optic nerve is, therefore, a critical component of the diagnosis of the disease.<sup>28</sup> Such an evaluation may be performed by observing the optic nerve head using an ophthalmoscope or by obtaining optic nerve head photographs. However, subjective identification



Figure 2. Schematic Illustration of Normal Anatomy and Neurodegenerative Changes Associated With Glaucomatous Optic Neuropathy



A, The optic disc is composed of neural, vascular, and connective tissues. The convergence of the axons of retinal ganglion (RG) cells at the optic disc creates the neuroretinal rim; the rim surrounds the cup, a central shallow depression in the optic disc. Retinal ganglion cell axons exit the eye through the lamina cribrosa (LC), forming the optic nerve, and travel to the left and right lateral geniculate nucleus, the thalamic relay nuclei for vision.

B, Glaucomatous optic neuropathy involves damage and remodeling of the optic disc tissues and LC that lead to vision loss. With elevated intraocular

pressure, the LC is posteriorly displaced and thinned, leading to deepening of the cup and narrowing of the rim. Distortions within the LC may initiate or contribute to the blockade of axonal transport of neurotrophic factors within the RG cell axons followed by apoptotic degeneration of the RG cells. Strain placed on this region also causes molecular and functional changes to the resident cell population in the optic nerve (eg, astrocytes, microglia), remodeling of the extracellular matrix, alterations of the microcirculation and to shrinkage and atrophy of target relay neurons in the lateral geniculate nucleus.

of optic disc damage from glaucoma can be challenging, with large disagreement in grading observed even among glaucoma specialists.<sup>29</sup> Several recently developed laser scanning imaging techniques provide more objective and quantitative information about the amount of optic nerve fiber (retinal ganglion cell axon) loss. These techniques, including confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography, have improved the identification of early disease and also enhanced the observation of progressive optic nerve fiber loss over time (Figure 4).<sup>30-34</sup>

Primary care physicians have an important role in the diagnosis of glaucoma by referring patients with a family history of glaucoma to undergo a complete ophthalmologic examination. Anyone with a family history of the disease and who has not had a dilated funduscopic examination of the optic nerve head in the past 2 years should be referred for examination. In addition, evaluation of the optic nerve with direct ophthalmoscopy performed by primary care physicians during a routine clinical visit, may reveal signs suspicious for optic nerve damage that should prompt referral to an ophthalmologist.<sup>11</sup>

**Treatment**

Slowing disease progression and preservation of quality of life are the main goals for glaucoma treatment. The decrease in quality of life associated with glaucoma may occur earlier than previously thought, underscoring the importance of early diagnosis and treatment.<sup>35</sup> Reduction of intraocular pressure is the only proven method to treat glaucoma.<sup>36</sup> Results from several multicenter clinical trials have demonstrated the benefit of lowering intraocular pressure in preventing the development and slowing the disease's progression (Table 1).<sup>37,38,40</sup> The Ocular Hypertension Treatment Study<sup>37</sup> randomized patients with ocular hypertension (high intraocular pressure but no clinical signs of glaucomatous damage to the optic nerve or visual field) to treatment vs no treatment. At the end of 5 years of follow-up, 4.4% of patients in the medication group vs 9.5% in the untreated group developed signs of glaucoma. The Early Manifest Glaucoma Trial<sup>38</sup> also randomized patients to treatment vs no treatment; however, all patients had a clear diagnosis of glaucoma at the baseline visit. After a median follow-up of 6 years, progression was less frequent in the treatment group (45%) than in the control group (62%).

Current management guidelines from the American Academy of Ophthalmology Preferred Practice Pattern recommend lowering the intraocular pressure toward a target level, which is a value or range of values at which the clinician believes that the rate of disease progression will be slowed sufficiently to avoid functional impairment from the disease.<sup>42</sup> Target intraocular pressure levels for a particular eye are established from pretreatment pressure levels that were associated with retinal damage, the severity of damage, risk factors for progression, life expectancy, and potential for adverse effects from treatment. In general, the initial target aims for a 20% to 50% reduction in pressure; however, the target pressure needs to be continuously reassessed during patient follow-up, depending on the evolution of the disease.<sup>42</sup> For example, if there is continued disease progression (optic nerve changes or visual field loss) despite pressure levels at the initial target value, the target will need to be lowered.

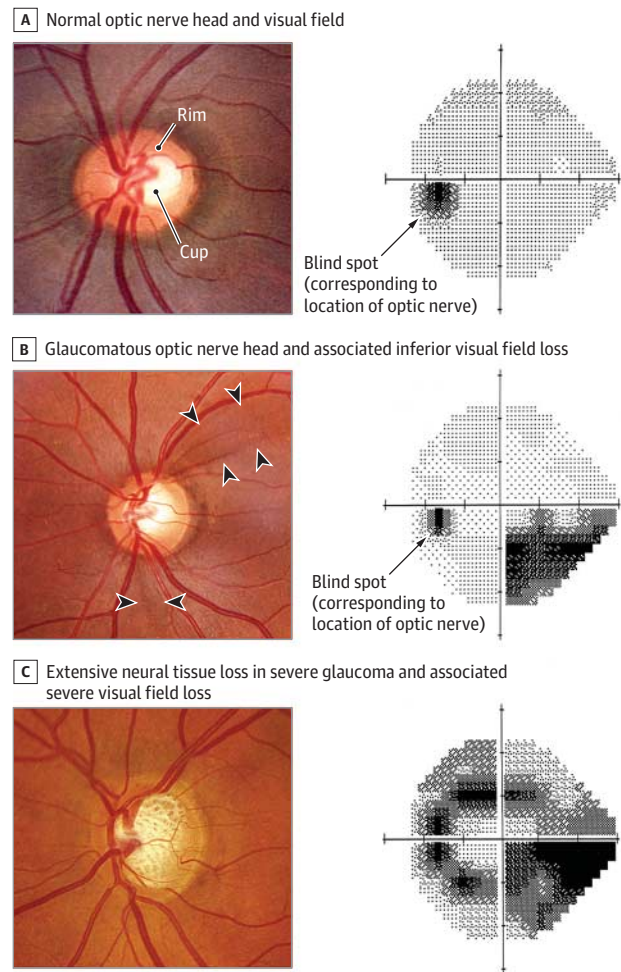
The target intraocular pressure should be achieved with the fewest medications and minimum adverse effects. Several different classes of pressure-lowering medications are available (Table 2). Medication choice may be influenced by cost, adverse effects, and dosing schedules. In general, prostaglandin analogues are the first-line of medical therapy. These drugs reduce intraocular pressure by reducing outflow resistance resulting in increased aqueous humor flow through the uveoscleral pathway.<sup>43</sup> These drugs are administered once nightly and have few, if any, systemic adverse effects. However, they can cause local adverse effects such as conjunctival hyperemia, elongation and darkening of eyelashes, loss of orbital fat (so-called prostaglandin-associated periorbitopathy), induced iris darkening, and periocular skin pigmentation.

Other classes of topical medications are less effective in lowering intraocular pressure than prostaglandin analogues.<sup>44</sup> They are used as second-line agents or when there is a contraindication or intolerance to the use of prostaglandin analogues (Table 2). Prostaglandin analogues and carbonic anhydrase inhibitors lower intraocular pressure during both the day and night. Other drugs such as the  $\beta$ -adrenergic blockers and  $\alpha$ -adrenergic agonists are effective only during the day and not at night.<sup>45</sup> Some of these agents, such as  $\beta$ -adrenergic blockers, may have significant systemic adverse effects and are contraindicated in patients with history of chronic pulmonary obstructive disease, asthma, or bradycardia. To decrease systemic absorption of topical medications, it is advisable for patients to use gentle punctal occlusion or eyelid closure for 2 minutes after drug instillation. General practitioners and internists should be aware that topical medications used by patients with glaucoma, including topical  $\beta$ -blockers, for example, may incur significant or even life-threatening adverse effects. Success of treatment can be enhanced by reinforcing the importance of compliance to the treatment regimen.

Considerable efforts have been made to develop neuroprotective glaucoma treatments that prevent optic nerve damage. Unfortunately, no good evidence exists that these agents can prevent disease progression in patients with glaucoma. In part, neuroprotection has not succeeded because of incomplete understanding of the pathophysiological mechanisms associated with optic nerve damage, the limited identification of drugs that can medicate the known pathways, and lack of a viable regulatory pathway for drug approval.<sup>46</sup>

When medical treatment does not achieve adequate intraocular pressure reduction with acceptable adverse effects, laser or in-

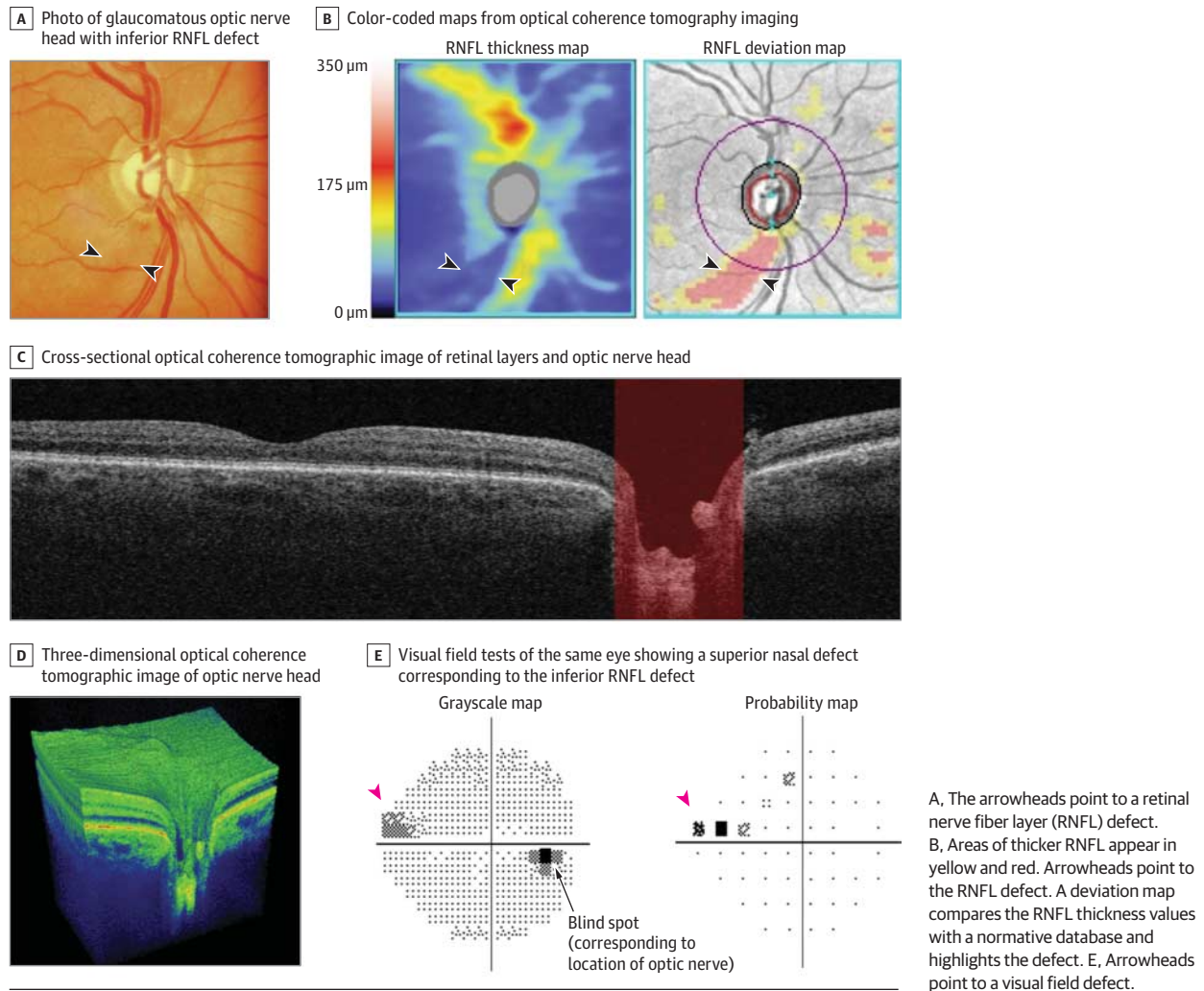
**Figure 3. Normal, Glaucomatous, and Severe Glaucomatous Optic Nerve Heads and Visual Field Test Results**



A, The pink area of neural tissue forms the neuroretinal rim, whereas the central empty space corresponds to the cup. B, Glaucomatous optic nerve showing loss of superior neural retinal rim (thinning) and excavation with enlargement of the cup. The arrowheads point to an associated retinal nerve fiber layer defect, which appears as a wedge-shaped dark area emanating from the optic nerve head. The superior neural losses correspond to the inferior defect (black scotoma) seen on the visual field. There is also a small retinal nerve fiber layer defect inferiorly, but the corresponding hemifield of the visual field remains within normal limits. C, More extensive neural tissue loss from glaucoma with severe neuroretinal rim loss, excavation, and enlargement of the cup. There is severe loss of visual field both in the superior as well as in the inferior hemifield.

cisional surgeries are indicated. The annual number of incisional glaucoma surgeries performed per million people in the United States has been estimated at 274.<sup>47</sup> In poorly adherent patients or in those with severe disease, surgery may sometimes be offered as a first-line therapy. Laser trabeculoplasty lowers intraocular pressure by inducing biological changes in the trabecular meshwork resulting in increased aqueous outflow. The procedure has an excellent safety profile and is performed during an office visit. Although substantial intraocular pressure reductions can be achieved in the majority of patients, the effect decreases gradually over time with a failure rate of about 10% per year.<sup>48-50</sup>

**Figure 4. Imaging Assessment of the Optic Nerve and Retinal Nerve Fiber Layer Using Spectral-Domain Optical Coherence Tomography**



Trabeculectomy is the most commonly performed incisional surgical procedure to lower intraocular pressure. It consists of excision of a small portion of the trabecular meshwork and or adjacent corneoscleral tissue to provide a drainage route for aqueous humor from within the eye to underneath the conjunctiva where it is absorbed. Antiscarring agents are frequently applied to the surgical site to decrease fibroproliferative response and increase success rates of the surgery, but may increase the rate of complications such as infection and damage from very low intraocular pressure. Devices that drain aqueous humor to an external reservoir are an alternative to trabeculectomy that are similarly effective in lowering intraocular pressure.<sup>51</sup> Several alternatives to these procedures have been proposed and are being investigated. These so-called minimally invasive glaucoma surgeries potentially incur less risk of sight-threatening complications.<sup>52</sup> To date, these procedures have not had the same intraocular pressure-lowering efficacy as trabeculectomy; however, they may be indicated for selected cases for which risk-benefit considerations are more favorable than those with trabeculectomy. A recent meta-analysis comparing trabeculectomy with nonpen-

etrating surgeries (deep sclerectomy, viscocanalostomy, and canaloplasty) concluded that while trabeculectomy was more effective in reducing the pressure, it carried a higher risk of complications.<sup>53</sup>

**Primary Closed-Angle Glaucoma**

The main feature distinguishing primary closed-angle glaucoma from primary open-angle glaucoma is that the angle, the site of aqueous outflow in the eye, is obstructed by apposition of the iris, resulting in an anatomically closed angle (defined if at least 270° of the angle is occluded). Like open-angle glaucoma, closed-angle glaucoma is predominantly an asymptomatic disease with individuals often unaware they have the disorder until advanced visual loss has occurred. In less than a third of cases, patients may present with acute primary angle closure, a clinical condition characterized by marked conjunctival hyperemia, corneal edema, a midilated unreactive pupil, a shallow anterior chamber, and very high intraocular pressure, usually greater than 30 mm Hg. Such patients often complain of ocular pain, nausea, vomiting, and intermittent blurring of vision with haloes noticed around lights.



Primary closed-angle glaucoma is caused by disorders of the iris, the lens, and retrolenticular structures. Pupillary block is the most common mechanism of angle closure and is caused by resistance to aqueous humor flow from the posterior to anterior chambers at the pupil. Aqueous humor accumulates behind the iris increasing its convexity causing angle closure (Figure 1). Nonpupil block mechanisms such as a plateau-like iris configuration may be responsible for a significant proportion of angle closure in Asian patients.<sup>54</sup> Closed-

**Table 1. Major Randomized Clinical Trials Evaluating the Role of Intraocular Pressure in Preventing or Delaying Glaucoma Development and Progression**

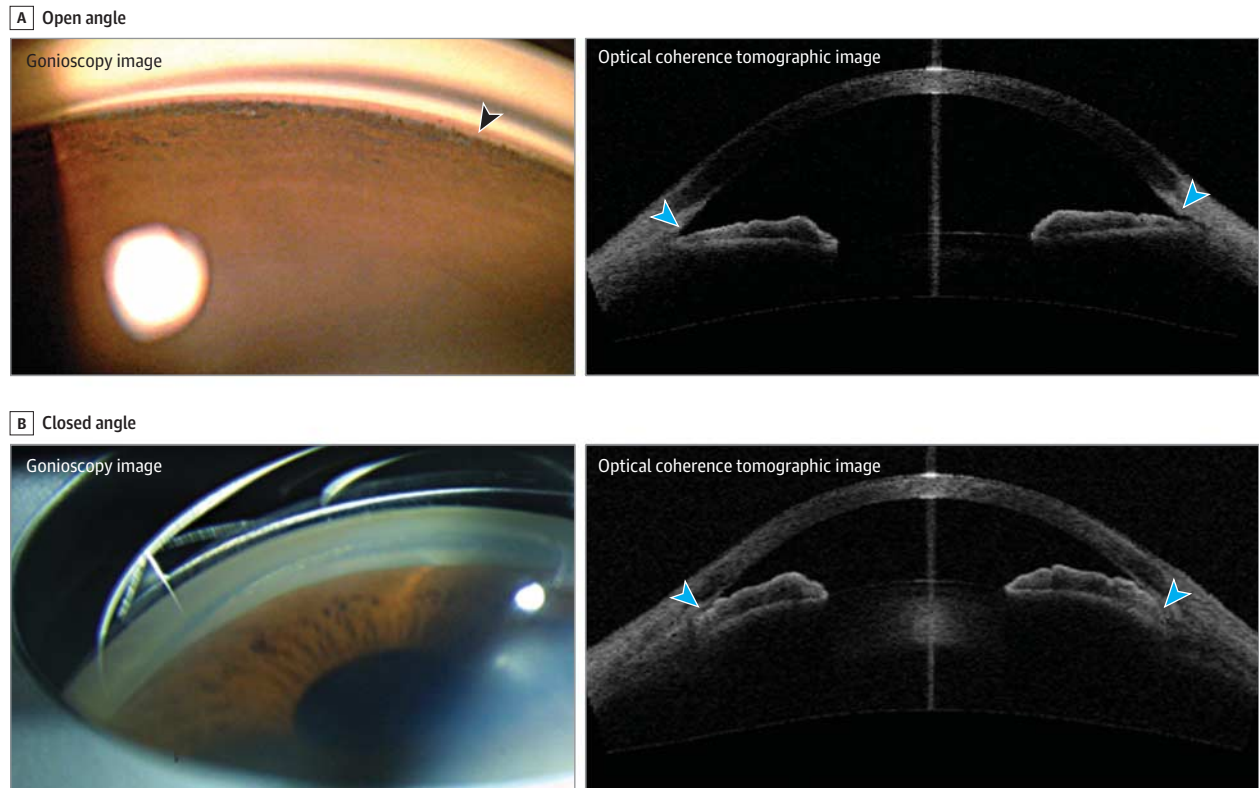
Clinical Trial	Purpose	Population	Design	Main Significant Outcomes
Ocular Hypertension Treatment Study, <sup>37</sup> 2002	To evaluate the safety and efficacy of ocular hypotensive treatment in preventing or delaying the onset of visual field or optic nerve damage	1637 Patients with ocular hypertension	Multicenter RCT comparing observation with medical therapy	Topical ocular hypotensive medication was effective in delaying or preventing the onset of primary open-angle glaucoma; the incidence of open-angle glaucoma after 60 mo of follow-up was 9.5% in the observation group vs 4.4% in the treated group
Early Manifest Glaucoma Trial, <sup>38</sup> 2002	To evaluate the efficacy of intraocular pressure reduction in preventing progression of glaucoma	255 Newly diagnosed patients with open-angle glaucoma	Multicenter RCT comparing observation with betaxolol and argon laser trabeculoplasty	At 6 y of follow-up, 62% of untreated eyes vs 45% of treated eyes showed progression; in multivariate analysis, progression risk was halved in the treatment group
Advanced Glaucoma Intervention Study, <sup>39</sup> 2000	To compare the clinical outcomes of 2 treatment sequences in glaucoma: trabeculoplasty-trabeculectomy vs trabeculectomy-trabeculoplasty-trabeculectomy	789 Eyes of 591 patients with medically uncontrolled open-angle glaucoma	Multicenter RCT comparing procedure sequences	Lower intraocular pressure was associated with less visual field loss during follow-up; eyes that had 100% of visits with intraocular pressure <18 mm Hg (average intraocular pressure during follow-up of 12.3 mm Hg) had significantly less visual field progression during follow-up
Collaborative Initial Glaucoma Treatment Study, <sup>40</sup> 2001	To compare medical vs surgical therapy as initial treatment	607 Patients with open-angle glaucoma	Multicenter RCT	Although intraocular pressure was lower in the surgical group, initial medical therapy resulted in similar visual field outcomes to the surgery group for up to 9 y of follow-up
Collaborative Normal Tension Glaucoma Study, <sup>41</sup> 1998	To determine if intraocular pressure plays a role in the pathogenesis of normal tension glaucoma	140 Eyes of 140 patients with normal tension glaucoma were defined as the median of baseline untreated intraocular pressure ≤20 mm Hg, with no measurement >24 mm Hg	One eye of each participant was randomized to be untreated as a control or to have intraocular pressure lowered by 30% from baseline	Twenty-eight (35%) of the control eyes and 7 (12%) of the treated eyes ( <i>P</i> < .001) had glaucoma progression during follow-up

Abbreviation: RCT, randomized clinical trial.

**Table 2. Classes of Medications Used to Lower Intraocular Pressure**

Class of Medication	Example	Usual Dosages	Mechanism of Action	Local Adverse Effects	Systemic Adverse Effects
Prostaglandin analogues (prostanamide)	Latanoprost, travoprost, tafluprost, unoprostone, bimatoprost	1/d At night	Increase in uveoscleral outflow of aqueous humor	Conjunctival hyperemia, lengthening and darkening of eyelashes, brown discoloration of the iris, uveitis, macular edema	Minimal systemic adverse effects; may be related to headaches
β-Adrenergic blockers	Timolol, levobunolol, carteolol, metipranolol, betaxolol	1/d In the morning	Reduction of aqueous humor production	Ocular irritation and dry eyes	Contraindicated in patients with asthma, chronic pulmonary obstructive disease, and bradycardia
α-Adrenergic agonists	Brimonidine, apraclonidine	3/d (Sometimes 2/d)	Initial reduction of aqueous humor production with subsequent effect of increase in outflow	Ocular irritation, dry eyes, allergic reaction is relatively common	Central nervous system effects and respiratory arrest in young children; caution in patients with cerebral or coronary insufficiency, postural hypotension, and renal or hepatic failure
Carbonic anhydrase inhibitors	Dorzolamide, brinzolamide, acetazolamide (oral)	3/d (Sometimes 2/d)	Reduction of aqueous humor production	Ocular irritation, dry eyes, burning sensation with topical agents	Topical form has minimal systemic adverse effects; oral form may be associated with paresthesia, nausea, diarrhea, loss of appetite and taste, lassitude, or renal stones
Cholinergic agonists	Pilocarpine, carbachol	Usually 4/d, but may vary	Increase in aqueous humor outflow	Ocular irritation, induced myopia and decreased vision due to ciliary spasm	Ciliary spasm leading to headaches in young patients

Figure 5. Gonioscopic Imaging and Optical Coherence Tomographic Imaging of Open-Angle and Closed-Angle



A lens with a prism is placed on the eye during gonioscopy, a process during which the examiner is able to examine the angle configuration and assess for the presence of angle closure. A, The arrowhead points to the lack of contact between the iris and angle. Image on the right shows the anterior segment captured by optical coherence tomography. The arrowheads point to visible

trabecular meshwork. B, The angle is closed with the trabecular meshwork not visible due to apposition of the iris to the angle. In the right image, the arrowheads indicate apposition of the iris to the angle wall; the anterior chamber is shallow and the iris has a slightly convex configuration. This is more noticeable in the region of the iris on the right.

angle glaucoma may also be caused by dynamic physiological factors, such as an increase in iris volume with pupil dilation and choroidal effusion.<sup>55</sup>

### Risk Factors

Risk factors for angle closure include female sex, older age, and Asian ethnicity (eg, Chinese). Eyes with angle closure tend to share certain biometric characteristics. The main ocular risk factor for angle closure involves having a crowded anterior segment in a small eye, with a shallow central anterior chamber depth, a thicker and more anteriorly positioned lens, and short axial length of the eye.<sup>55-57</sup> With anterior segment optical coherence tomography, other anatomical risk factors for angle closure have been recently identified such as smaller anterior chamber width, area and volume, thicker irides with greater iris curvature, and a greater lens vault.<sup>57</sup>

### Genetics

A genetic etiology for angle closure is supported by epidemiological findings: first-degree relatives of patients with it are at greater risk than the general population, the high heritability of anatomical risk factors (such as anterior chamber depth), and ethnic variations in the prevalence.<sup>58,59</sup> Recently, a genome-wide association study involving more than 20 000 individuals from 7 countries found 3 new genetic loci for angle closure: rs11024102 at *PLEKHA7*, rs3753841

at *COL11A1* (HGNC:2186), and rs1015213 located between *PCMTD1* (HGNC:30483) and *ST18* (HGNC:18695) on chromosome 8q.<sup>59</sup> This indicates that open-angle and closed-angle glaucoma are distinct genetic entities with different genes associated with each disease.

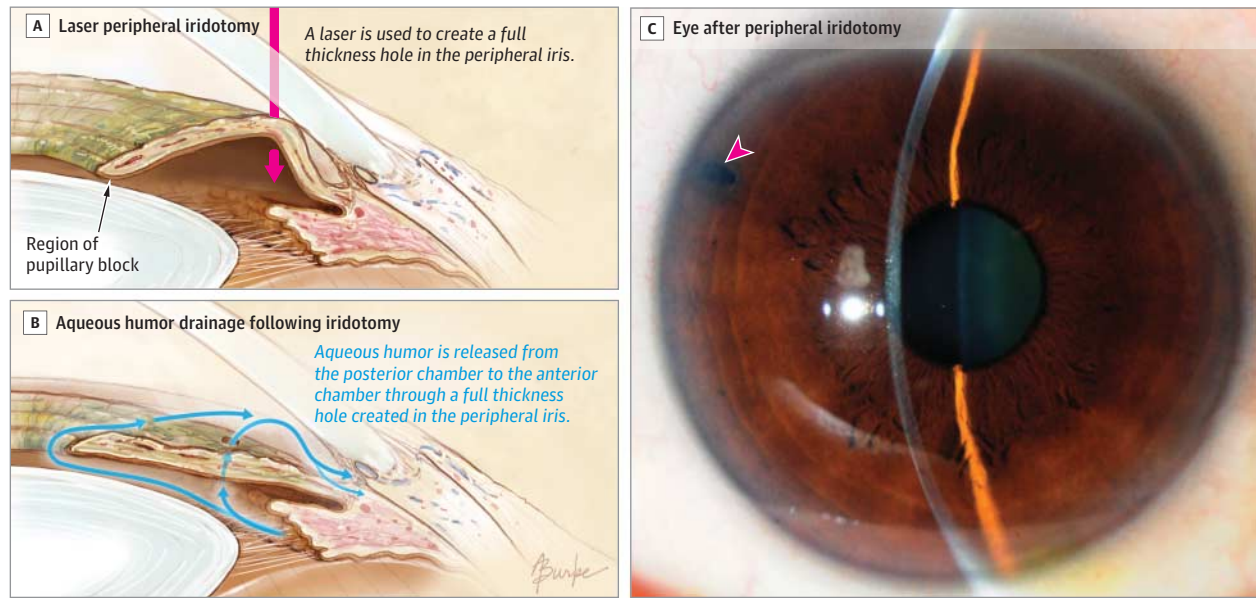
### Clinical Presentation and Diagnosis

The distinctive clinical features of angle closure are observed in the angle of the eye by gonioscopy. A simple, handheld, mirrored instrument is placed on the patient's eye, followed by examination of the angle using a slit-lamp biomicroscope (Figure 5). With indentation, the examiner is also able to determine if peripheral anterior synechiae (adhesions between the iris and trabecular meshwork) are present. Gonioscopy is highly subjective, with poor reproducibility, and gonioscopic findings may vary with the amount of light used during the examination or mechanical compression of the eye.

Several imaging methods have been recently developed that can be used to objectively assess eyes for the presence of angle closure. Ultrasound biomicroscopy allows for the acquisition of real-time images of the angle, with resolution of between 25  $\mu$ m to 50  $\mu$ m.<sup>60</sup> With biomicroscopy, one is able to visualize posteriorly located structures such as the ciliary body, lens zonules, and the anterior choroid, making it useful for identifying specific causes of angle closure. Biomicroscopic imaging requires a skilled operator and cooperation from patients during the imaging. Anterior segment op-



Figure 6. Closed-Angle Glaucoma Treatment by Laser Peripheral Iridotomy



C, Arrowhead points to the full-thickness hole in the iris.

tical coherence tomography is a noncontact imaging device that acquires high-resolution cross-sectional images of the anterior chamber (Figure 5). The incorporation of automated image analysis software allows for rapid measurement of anterior segment parameters. Comparison studies found a higher rate of diagnosis of closed angles with tomography than with gonioscopy.<sup>61</sup>

### Management

The management of patients with angle closure depends on the stage of disease and on correctly identifying the underlying mechanism. The first-line treatment of angle closure is laser peripheral iridotomy, a procedure in which a full thickness hole is created in the iris (Figure 6) to eliminate pupillary block. This procedure is generally easily performed in the office without adverse events. Rare complications of iridotomy include transient increases of intraocular pressure, cornea decompensation, posterior synechiae (adhesions of iris to lens) formation, and optically induced visual disturbances. Eyes treated with iridotomy may still develop increased pressure over time; thus, it is essential to have periodic follow-up after the procedure. Studies suggest that iridotomy is most effective in decreasing pressure in the early stages of disease, but once extensive synechial angle closure and glaucomatous optic neuropathy have developed, its effect is more subdued.<sup>62</sup> If pressure remains high after iridotomy, long-term medical treatment (including topical  $\beta$ -blockers,  $\alpha_2$ -agonists, carbonic anhydrase inhibitors, and prostaglandin analogues) can be instituted, similar to the management of open-angle glaucoma.

#### Acute Primary Angle Closure

Acute primary angle closure is an ocular emergency and requires immediate management to avoid blindness. Patients usually present with a painful red eye associated with blurring of vision, headache, and nausea and vomiting. The cornea is usually hazy due to the very high intraocular pressure, and the pupil is frequently mid-dilated and

poorly reactive to light. The aims of the treatment are to achieve rapid pressure control with topical and systemic medications to limit optic nerve damage. This is followed by iridotomy to alleviate pupillary block. Iridotomy successfully aborts the attack in 42% to 72% of cases, and many patients recover without optic disc or visual field damage if the pressure is promptly and adequately controlled.<sup>63</sup> Laser iridoplasty (contraction of the peripheral iris) can be performed if conventional medical treatment is not tolerated or does not abort the attack. If iridotomy is unsuccessful or difficult to perform because of a cloudy cornea, surgical iridectomy is indicated. Prophylactic iridotomy should be carried out for the fellow eye, which is at high risk of acute angle closure.

#### Angle Closure Suspects

Management of patients suspected of having angle closure and who do not have glaucoma (ie, anatomically narrow angles but normal intraocular pressure and optic discs) is aimed at modifying the anterior segment configuration, before development of irreversible trabecular meshwork damage and glaucomatous optic neuropathy. The current practice is to offer prophylactic iridotomy to such patients, especially in the presence of risk factors such as a family history of angle closure, and those with symptoms or signs suggestive of intermittent acute angle closure, those who require repeated dilatation (such as diabetics), or for patients who lack access to medical care or are available for limited follow-up care. Cataract extraction with intraocular lens implant is an alternative to iridotomy in those with visually significant cataract because the surgery can decrease intraocular pressure and also widens the angles, thereby improves vision.

#### Surgical Management

As in primary open-angle glaucoma, surgical management is indicated when there is inadequate intraocular pressure lowering or is indicated for those with progression of optic nerve or visual field

damage despite medical and laser treatment. Trabeculectomy, either alone or in combination with lens extraction should be considered if the pressure control remains too high despite laser and medical treatment, especially in more advanced cases of open-angle glaucoma. Lens extraction is also performed when lens-related mechanisms predominate, especially in cases in which a significant cataract impairs vision. Finally, glaucoma drainage implants may be used in patients with chronic angle closure similarly to open-angle glaucoma when trabeculectomy has failed to control pressure, or in eyes that are deemed to be at high risk of failure with trabeculectomy.

## Conclusions

Glaucoma is a leading cause of blindness. Early diagnosis and treatment can prevent vision loss from the disease. Primary care physicians should consider referring patients with a family history of the disease for a complete ophthalmologic examination. In addition, evaluation of the optic nerve by direct ophthalmoscopy may identify suspicious signs of optic nerve damage that should also prompt referral to an eye care specialist.

### ARTICLE INFORMATION

**Author Contributions:** Drs Weinreb, Aung, and Medeiros had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** All authors.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** All authors.

**Critical revision of the manuscript for important intellectual content:** All authors.

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**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Weinreb reported that he has worked as a consultant for Alcon, Allergan, Anakem, Aquesys, Bausch and Lomb, Carl Zeiss Meditec, Quark, Sensimed, Solx, Topcon and has received research support from National Eye Institute, Nidek, Genentech, Quark, and Topcon. Dr Aung reported that he has worked as a consultant for Alcon, Allergan, Bausch and Lomb, MSD, and Quark; has received research support from Alcon, Allergan, Aquesys, Carl Zeiss Meditec, Ellex, and Ocular Therapeutics; and has received lecture fees from Alcon, Allergan, Carl Zeiss Meditec, Ellex, Pfizer, and Santen. Dr Medeiros reported that he has received research support from the National Eye Institute, Alcon, Allergan, Merck, Carl-Zeiss Meditec, Heidelberg Engineering, Sensimed, and Reichert.

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**Submissions:** We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at [mdm608@northwestern.edu](mailto:mdm608@northwestern.edu).

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