Clinical trials: correct formulation of research question important when conducting randomized controlled trial (RCT); most glaucoma trials of last few decades still relevant; some authors reluctant to refute their previous views; data analyzed differently by different people and interpretation subjective; post hoc studies of data from RCTs sometimes make inaccurate or controversial conclusions.

Trials in glaucoma: in late 1980s, no RCT had proven that lowering intraocular pressure (IOP) benefits patients with primary open-angle glaucoma (POAG); since then, 6 large RCTs studied patients at different stages of disease; Ocular Hypertension Treatment Study (OHTS) and Collaborative Normal Tension Glaucoma Study (CNTGS) evaluated percentage reduction in IOP; Advanced Glaucoma Intervention Study (AGIS) used single target level of IOP; Collaborative Initial Glaucoma Treatment Study (CIGTS) used specific formula for target IOP for each patient; Early Manifest Glaucoma Trial (EMGT) and European Glaucoma Prevention Study (EGPS) used treatment algorithms.

Glaucoma: continuum of disease; few patients in industrialized countries experience functional impairment; many patients treated to benefit few because identification of high-risk patients not possible; treatments overly aggressive for some patients and inadequate for others.

Collaborative Normal Tension Glaucoma Study: design — studied patients with advanced disease; assessed whether therapy to lower IOP therapy appropriate in normal-tension glaucoma (NTG); 145 patients randomized to medication, laser, and surgery vs no treatment; eligibility criteria required use of 3 medicines for glaucoma, IOP ≥18 mm Hg, and damage to optic nerve; patients randomized to initial treatment with laser vs surgery (argon laser trabeculoplasty or trabeculectomy); contemporary practice does not include laser therapy for patients in whom trabeculectomy fails; results — surgical patients achieved lower IOPs; black patients initially treated with laser had better preservation of vision, probably because laser more effective in pigmented eyes; trabeculectomy less effective in patients of African descent; post hoc predictive analysis — conducted by pooling treatment groups to assess relationship of progression to IOP; study measured IOP every 6 mo for 8 yr; patients with IOP <14 mm Hg (based on mean of measurements at 6, 12, and 18 mo) had better outcomes; although patients with highest IOPs worsened, progression slow over decade of study; post hoc associative analysis — showed that, when IOP <18 mm Hg throughout 8-yr period of study, patient unlikely to progress; although mean IOP 12.3 mm Hg in this subgroup, this does not indicate IOP must be lowered to 12.3 mm Hg (doing so often constitutes overtreatment); another post hoc analysis — poor prognosis more strongly associated with greater standard deviation (SD) of IOP than with mean IOP; however, study evaluated long-term variability rather than more important intraday variability and did not control for fact that treatment introduces long-term variability.

Educational Objectives
The goals of this program are to improve diagnosis and treatment of glaucoma. After hearing and assimilating this program, the clinician will be better able to:

1. Summarize the findings of major trials in glaucoma.
2. Monitor glaucomatous cupping and visual field abnormalities in patients of Asian descent.
3. List risk factors for glaucoma in patients with ocular hypertension.
4. Describe the limitations of some of the recent major trials in glaucoma.
5. Counsel a patient with ocular hypertension who has developed glaucoma about treatment options.

Faculty Disclosure
In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, the following has been disclosed: Dr. Singh is a consultant for Alcon, Aerie Pharmaceuticals, Allergan, AMO, Carl Zeiss, ForSight VISION5, InFocus Inc, Ivantis, Santen Pharmaceutical Co, and Transcend Medical. The planning committee reported nothing to disclose.
Interpretation: cause of worsening (variability in IOP vs high IOP) remains unclear; retrospective analyses can demonstrate association but not causation; AGIS showed that trabeculectomy more effective than laser trabeculoplasty for lowering IOP, and that maintaining IOP <18 mm Hg may be beneficial; however, most patients do not need to achieve IOP of 12.3 mm Hg; when selecting treatment, surgeon must consider life expectancy of patient and stage of disease.

Ocular Hypertension Treatment Study: design — studied >1600 patients with high IOP, normal optic nerves, and normal visual fields; eligibility criteria required IOP 24 to 32 mm Hg in one eye and ≥21 mm Hg in fellow eye; patients randomized to medications to achieve lowering of IOP by 20% vs no treatment; results — untreated patients had twice rate of conversion to glaucoma; treating intraocular hypertension reduced development of glaucoma; absolute reduction in risk 5% (over 5 yr, glaucoma developed in 10% of untreated and 5% of treated patients); surgeon must treat 20 patients for 1 to benefit.

Risk factors for worsening: include older age, thinner corneas, poorer visual fields, and larger optic nerve cups; when patients with field loss and large cups omitted from analysis, risk for glaucoma in untreated patients <10%; ethnicity — not identified as risk factor for glaucoma; in OHTS, after correcting for central corneal thickness, IOP, and cup-to-disc ratio, ethnicity no longer associated with glaucoma; however, risk factors may differ depending on stage of disease; although likelihood of progression from ocular hypertension to glaucoma may not be associated with race, blacks with glaucoma have higher risk for blindness; family history — not identified as risk factor; however, family history obtained from unvalidated patient report; diabetes mellitus (DM) — appeared protective, but this finding not confirmed when data combined with data from EGPS; protective effect probably observed because patients with diabetic retinopathy excluded from study (ie, study participants represented healthy group of patients with DM, who may have engaged in especially healthful behaviors that influenced progression); also, autoregulatory phenomena at optic nerve head may take place in early stages of DM, such that some parts of retina and ganglion cells sacrificed to preserve optic nerve function.

Important findings and conclusions: most important contribution of OHTS ability to identify high-risk patients; with IOP >25.75 mm Hg and corneal thickness <555 μm, risk for glaucoma shown to be 36%, confirming that patients with thinnest corneas and highest IOPs should be treated first; whether effect of treatment different in high-risk group vs other patients remains unknown; patients in study who had cataract surgery had decrease of >3 mm Hg in IOP for 36 mo; removing cataracts important component of treatment in many patients; from public health perspective, treating cataracts may be more useful for preserving vision than identifying and treating glaucoma; interpretation — OHTS showed that measuring central corneal thickness important for improving estimation of IOP, lowering IOP reduces risk for disease and progression, and cataract surgery lowers IOP; in future, cataract surgery likely to be performed earlier in patients with glaucoma; performing cataract surgery before trabeculectomy decreases likelihood of bleb failure; limitations — accrual of patients insufficient to allow assessment of risk reduction in subgroups; effect of treating ocular hypertension on development of blindness undetermined.

Early Manifest Glaucoma Trial: design — evaluated advisability of therapy to lower IOP in newly diagnosed asymptomatic patients with nerve damage or field loss; results — over one decade, control group more likely to worsen than patients treated with laser and betaxalol; risk factors for progression — higher baseline IOP, higher IOP on treatment, exfoliation syndrome, disc hemorrhage, aging, and bilateral disease; in this study, no variability introduced by subsequent therapy after initial treatment; worsening associated with mean IOP but not with variability of IOP; low blood pressure — shown in 8 major trials and surveys to be risk factor for progression of glaucoma; however, patients who have low blood pressure because of healthy behaviors may differ from those with low blood pressure induced by antihypertensives; patients on antihypertensives may have poor circulation and hypoperfusion; overtreating systemic hypertension may be undesirable; interpretation — EMGT showed that lowering IOP beneficial; for patients with IOP between 18 and 22 mm Hg, each millimeter of mercury reduction in IOP resulted in 10% reduction in risk for glaucoma; mean IOP more important risk factor than variability of IOP.

Collaborative Initial Glaucoma Treatment Study: design — studied newly diagnosed glaucoma; patients had slightly more severe disease than those in EMGT; patients randomized to initial treatment with medication vs trabeculectomy; trabeculectomy group treated with laser second and medication third, if needed; this treatment algorithm not used in practice; most patients who had initial trabeculectomy did not need further treatment; primary outcome change in visual fields; study also evaluated visual acuity, changes in IOP, quality of life, and formation of cataracts; target IOP individualized based on baseline IOP and visual field score; results — compared with surgical group, IOP in medication group 2 to 5 mm Hg higher at all time points; at 18 mo, surgical group had greater lowering of IOP but study found no difference between groups in visual field scores; lower IOP in surgical group did not translate into visual benefit; reductions in IOP 46% in surgical group and 38% in medical group; study showed that lowering IOP into low- to midteens beneficial; further lowering of IOP probably offers no benefit; visual preservation similar between groups; surgical group had greater loss of visual acuity due to cataracts and more initial ocular symptoms.

Implications: in developed world, surgery reserved for patients without adequate response to medications and laser, but in developing world (in which medications scarce), study confirms that initial surgery as effective as initial medication; based on quality-of-life measures in CIGTS, initial medication superior to initial surgery; additional lowering unimportant after IOP significantly reduced; importance of long-term variability in IOP probably related to relationship between IOP and loss of ganglion cells; when patients from AGIS reanalyzed after removing those who had >1 procedure, variability only important when mean IOP low; variability in results may reflect inclusion of patients at different stages of disease; other patients remains unknown; patients in study who had cataract surgery had decrease of >3 mm Hg in IOP for 36 mo; removing cataracts important component of treatment in many patients; from public health perspective, treating cataracts may be more useful for preserving vision than identifying and treating glaucoma; interpretation — OHTS showed that measuring central corneal thickness important for improving estimation of IOP, lowering IOP reduces risk for disease and progression, and cataract surgery lowers IOP; in future, cataract surgery likely to be performed earlier in patients with glaucoma; performing cataract surgery before trabeculectomy decreases likelihood of bleb failure; limitations — accrual of patients insufficient to allow assessment of risk reduction in subgroups; effect of treating ocular hypertension on development of blindness undetermined.

European Glaucoma Prevention Study: design — goal to assess whether treating ocular hypertension decreases likelihood of conversion to glaucoma; unlike OHTS, placebo group included; study enrolled patients ≥30 yr of age with IOP 22 to 29 mm Hg; in contrast, OHTS included patients ≥40 yr of age with IOP 24 to 32 mm Hg; patients had normal visual fields and normal optic nerves; treated group received dorzolamide 3 times daily; placebo group received vehicle for dorzolamide; dorzolamide not usual first-line agent; results — large placebo effect and small but significant difference in reduction in IOP documented; no significant difference seen between groups in proportion of eyes developing POAG; limitations — 30% of patients dropped out; compared with patients who completed study, IOP 2 mm Hg higher in patients who withdrew; findings suggest that investigators withdrew patients because of concerns about rising IOP, at 6 mo, reduction in IOP 14.5% in dorzolamide group and 9% in placebo group; at 60 mo, reduction in IOP 22% in dorzolamide group and 18% in placebo group; large observed decreases in IOP reflect withdrawal of patients with higher IOPs; study used single measurement of IOP at baseline rather than averaging multiple measurements; therefore, patients in study may have had lower mean IOP at baseline than that reported by study, and decrease in IOPs during study could have represented regression to mean.
Dr. Singh was recorded at the progression in the early manifest glaucoma trial. Bengtsson B et al: Summary of Medicine. For information about courses sponsored by Loyola University Chicago Stritch School of Medicine, please visit http://...

...ervation demonstrated; OHTS — showed that central corneal thickness important and clarified risk factors; among these studies, OHTS had greatest influence on practice because it led to measurement of central corneal thickness; EGPS — provides example of flawed study conduct.

Implications for practice: in developed countries, 25% to 50% of people with glaucoma aware of their disease, and of these, only half receive regular care; most people with undiagnosed glaucoma do not lose vision; lowering IOP reduces but does not eliminate risk; although patients who progress quickly need aggressive intervention, many do well without treatment; encourage regular follow-up (good visual outcomes more strongly associated with regular surveillance than with refilling medications); regular examinations permit early treatment of patients with aggressive disease; failure to fill medications not correlated with failure to present for follow-up visits.

Suggested Reading

Acknowledgments
Dr. Singh was recorded at the Eighth Annual Glaucoma/Cataract Symposium, sponsored by Loyola University Chicago Stritch School of Medicine. For information about courses sponsored by Loyola University Chicago Stritch School of Medicine, please visit http://somas.luc.edu/cme/. The Audio Digest Foundation thanks Dr. Singh and the Loyola University Chicago Stritch School of Medicine for their cooperation in the production of this program.

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THE INFLUENCE OF LANDMARK GLAUCOMA TRIALS ON CLINICAL PRACTICE

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1. Which of the following studies used a specific formula to identify a target intraocular pressure (IOP) for each individual patient?
   (A) Ocular Hypertension Treatment Study (OHTS)
   (B) Collaborative Normal-Tension Glaucoma Study (CNTGS)
   (C) Advanced Glaucoma Intervention Study (AGIS)
   (D) Collaborative Initial Glaucoma Treatment Study (CIGTS)**

2. Which of the following was a finding of CIGTS?
   (A) 57% of patients required trabeculectomy
   (B) β-blockers may worsen normal-tension glaucoma (NTG)
   (C) Many patients with NTG may be followed conservatively **
   (D) Asian descent was a risk factor for progression to glaucoma

3. Which of the following is a probable explanation for cupping and visual field abnormalities commonly seen in young Asian patients?
   (A) Cataracts (C) Low incidence of diabetes
   (B) Low blood pressure (D) Myopia

4. Post hoc analyses of AGIS showed which of the following?
   (A) Increased variability of IOP was associated with poor prognosis **
   (B) Long-term variability in IOP was less important than intraday variability
   (C) IOP should be lowered to 12.3 mm Hg
   (D) IOP at baseline was not related to disease progression during the study

5. In OHTS, which of the following was a risk factor for glaucoma?
   (A) Ethnicity (C) Family history
   (B) Corneal thickness ** (D) Diabetes

6. Which of the following summarizes the major finding of OHTS?
   (A) Risk reduction was similar in all subgroups
   (B) Treating ocular hypertension prevents blindness
   (C) Treatment is indicated for patients with the thinnest corneas and highest IOPs
   (D) For preventing blindness, treating cataracts is more important than identifying and treating glaucoma

7. Which of the following were findings of the Early Manifest Glaucoma Trial?
   1. Treatment with laser and betaxolol is superior to observation in patients with early glaucoma
   2. Baseline IOP was associated with progression of disease
   3. The variability of IOP was associated with progression of disease
   4. Treating ocular hypertension reduces the risk for glaucoma
   (A) 1,2 ** (B) 1,3 (C) 1,2,3,4 (D) 2,3,4

8. Which of the following was a limitation of CIGTS?
   (A) The treatment algorithm used in the study is not commonly used in clinical practice
   (B) The efficacy of medication was not adequately evaluated because most patients did not need further treatment after trabeculectomy
   (C) The study did not evaluate the influence of cataracts
   (D) The target IOP was undefined

9. In CIGTS, initial treatment with medication was believed to be superior to initial treatment with surgery based on measures of:
   (A) Visual fields (C) Loss of retinal ganglion cells
   (B) Safety (D) Quality of life

10. Which of the following is true of patients who were enrolled in the European Glaucoma Prevention Study?
    (A) Older than patients enrolled in OHTS
    (B) Baseline IOPs were 24 to 32 mm Hg
    (C) Some received a placebo
    (D) The active treatment group received agents typically used as first-line therapy for glaucoma