

# Landmark Glaucoma Studies

Key Findings and Treatment Lessons

By Annie Stuart, Contributing Writer

In the past few decades, glaucoma research has produced a veritable alphabet soup of clinical trials, from AGIS to TVT. These landmark randomized studies have greatly deepened knowledge of the disease. Six leading investigators highlight key findings from these studies and the impact on their clinical practice. We share some of the important lessons here.



# Ocular Hypertension Treatment Study

## LINKING IOP AND ONSET OF GLAUCOMA

### KEY FINDINGS

**Treatment delays onset of glaucoma.** A pioneer among glaucoma trials, OHTS was the first to demonstrate clearly that treating abnormally elevated intraocular pressure (IOP) with topical medications delays or prevents the onset of glaucomatous damage. A second goal of the study, said Michael A. Kass, MD, OHTS principal investigator, was to identify baseline demographic and clinical risk factors for developing primary open-angle glaucoma (POAG).

At five years, treatment with topical antiglaucoma medication decreased IOP by 20 percent and reduced the incidence of glaucoma by 60 percent compared with observation.<sup>1</sup>

**Ten-year follow-up shows reduced incidence.** “To aid management, we thought it would be helpful for clinicians and patients to know the 10-year incidence of glaucoma in treated and untreated

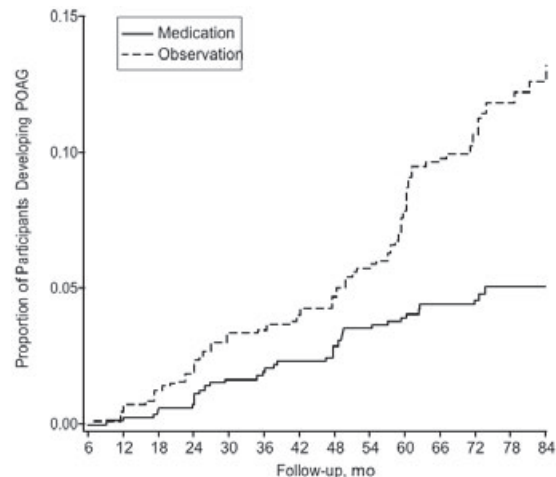
ocular hypertensives,” said Dr. Kass, professor and chairman of ophthalmology and visual sciences at Washington University in St. Louis.

In looking at the 10-year data, the investigators used baseline risk factors such as IOP, age, central corneal thickness, vertical cup-to-disc ratio, and pattern standard deviation to establish low-, medium- and high-risk groups. The 10-year incidence of glaucoma was roughly linear, with treatment reducing it by about 50 percent in all three levels of risk, said Dr. Kass. However, the absolute reduction was greatest in the high-risk group (from 42 to 19 percent) and least in the lowest-risk group (from 7 to 4 percent). African-American

patients showed a similar treatment effect, after adjustment for their higher baseline risk.

### LESSONS FOR CLINICIANS

**Take risk categories into account.** From this study, investigators concluded that it is possible to separate ocular hypertensive patients into categories of high, medium and low risk. “The ocular hypertensive patients at high risk may benefit from close



Kaplan-Meier plot depicts cumulative probability of POAG developing over time in the treated and untreated ocular hypertension groups.

follow-up and some from early treatment,” said Dr. Kass, “whereas the low-risk patients can have less frequent follow-up and may not need early treatment.” This decision, he said, depends upon individual factors such as age, health status, life expectancy and patient preference.

**Consider observation before treatment in some patients.** Douglas R. Anderson, MD, professor emeritus at Bascom Palmer Eye Institute who was also involved with OHTS, said that this trial attempted to resolve a decades-long debate: Should ocular hypertensives be treated in an attempt to prevent the onset of glaucoma? Or should they be closely watched and treated only after the first signs of glaucoma emerge?

“The rationale for the latter approach is that only 10 or 20 percent of people with ocular hypertension eventually develop glaucoma, so you’d be treating about 80 percent unnecessarily,” he said. “They’d ‘enjoy’ the side effects of treatment without getting any benefit.” Given that glaucoma can be well managed without major visual loss in early stages, Dr. Anderson often opts for observation. Another advantage, he said, is that delaying treatment sometimes means that better treatments become available in the interim.

*NOTE: References for all studies discussed in this article appear on page 54.*

### OHTS AT A GLANCE

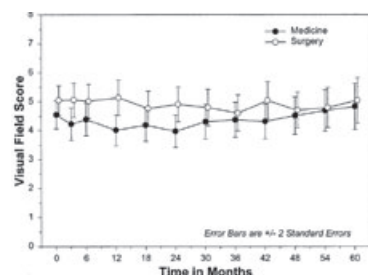
- 10 years of follow-up
- 1,636 patients with ocular hypertension
- Entry criteria: ages 40 to 80; normal visual fields and normal optic discs; untreated IOP of 24 to 32 mmHg in one eye, 21 to 32 mmHg in fellow eye
- Initially randomized to observation or a stepped topical medical regimen; patients in observation group offered medication after 7.5 years of follow-up
- Main outcome measure: visual fields and stereoscopic optic disc photographs<sup>1</sup>

# Collaborative Initial Glaucoma Treatment Study

## TRABECULECTOMY VS. DRUGS FOR INITIAL THERAPY

### KEY FINDINGS

**Aggressive IOP targets yield results.** The CIGTS set an aggressive target IOP for each patient, according to baseline characteristics, and substantial and sustained IOP reduction was achieved in both treatment arms: roughly 35 percent with medication and 48 percent with surgery.<sup>2</sup> The medication arm



Visual field scores over time in the overall medication and surgery groups did not reveal the differences seen in subgroup analyses.

used a stepped regimen of topical medications, beginning with a single agent and adding drugs if target IOP was not achieved or if visual field loss progressed. In the surgical arm, trabeculectomy was performed. In

either arm, if treatment failed, the patient received argon laser trabeculoplasty (ALT).

**Quality of life measured.** Although visual fields were the primary outcome measure, the CIGTS was the first clinical glaucoma trial to include quality of life as an important outcome variable, said the study chairman, Paul R. Lichter, MD, director of the University of Michigan Kellogg Eye Center in Ann Arbor.

### LESSONS FOR CLINICIANS

**Discuss fear of blindness.** “CIGTS found that fear of blindness in newly diagnosed glaucoma patients is a very important topic for ophthalmologists to address directly,” said Dr. Lichter. “Thus, I have made it a point to be especially sensitive to this finding and to reassure patients that, with appropriate follow-up and management, the chance of blindness from glaucoma is not great, especially if the disease is not advanced at the time of diagnosis.”

**Consider surgery first in patients with moderate or advanced disease.** Although previous studies from England and Scotland had supported early surgery, said Dr. Lichter, interim results from CIGTS showed no such advantage overall. However, later subgroup analysis revealed differences: Patients with moderate or advanced disease at the time of

diagnosis had better results with surgery than with medication as initial treatment. Specifically, those who had a mean deviation of  $-10$  dB or worse on the Humphrey Field Analyzer were more likely to show visual field progression if initially treated with medicine.

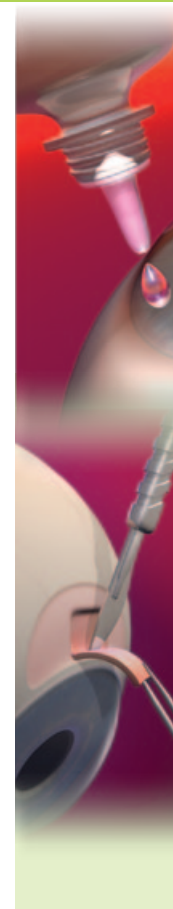
This has led Dr. Lichter to encourage early surgery for Caucasian patients with moderately extensive visual field loss at the time of diagnosis, although medication is his preference for initial treatment of most mild cases. Similarly, this “intriguing finding” has influenced the practice of Steven J. Gedde, MD, professor of ophthalmology at Bascom Palmer Eye Institute, who said, “I have a lower threshold for surgical intervention in patients with moderate to severe glaucoma.”

**But remember the exceptions.** Still, the investigators found surprising exceptions: African-Americans patients do not fare as well as white patients with the surgery-first approach. Also, Dr. Lichter said, “We found that patients with diabetes mellitus also do not do as well with initial surgery.”

**Filtering surgery is easier before eyedrops are used.** Although not an official measure in the CIGTS trial, surgeons reported that the pristine conjunctiva in patients who had not previously used eyedrops made filtering surgery technically easier than in patients who had used eyedrops prior to surgery.

**Keep IOP steady.** CIGTS data showed that high IOP variability is unfavorable for glaucoma patients and that variability is greater with use of drops than after surgery. “I, therefore, emphasize to my patients that one of the goals of therapy is to maintain as steady a level of IOP as we can,” Dr. Lichter said. Initial surgery tends to protect against spikes and maximum IOP, which are important predictors of future visual field loss.

**Major surgical complications are few.** Although there were frequent minor complications right after trabeculectomy, CIGTS showed that few were serious, and all resolved without sequelae. The risk of endophthalmitis was less than 2 percent over seven years.



### CIGTS AT A GLANCE

- Five to nine years of follow-up
- 607 patients, aged 25 to 75, with newly diagnosed open-angle glaucoma (OAG)
- Entry criteria: IOP of 20 mmHg or greater; optic nerve damage and/or visual field loss in one or both eyes
- Randomized to initial treatment with stepped topical medication or trabeculectomy
- Main outcome measure: visual fields<sup>3</sup>

# Early Manifest Glaucoma Trial

## TREAT IOP EARLY, FOLLOW PROGRESS CLOSELY

### KEY FINDINGS

**Treatment effect validated.** The goals of the EMGT were twofold: to compare the effect of IOP-lowering treatment versus observation on the progression of early, newly detected untreated glaucoma and to assess the magnitude of any treatment effect.

“EMGT offers the most solid proof we have today that pressure lowering is beneficial in glaucoma treatment, in all clinical situations,” said Anders Heijl, MD, PhD, who was EMGT study director and is professor and chairman of ophthalmology at Malmö University Hospital, University of Lund, in Sweden. He added that these findings are consistent with OHTS and CNTG studies.

**Every 1 mmHg reduction matters.** “Among the EMGT subjects, some had more IOP lowering than others,” said Dr. Anderson, of Bascom Palmer, “and those with the greatest IOP lowering enjoyed the most benefit.” Dr. Heijl said that he was surprised by the magnitude of the treatment effect:

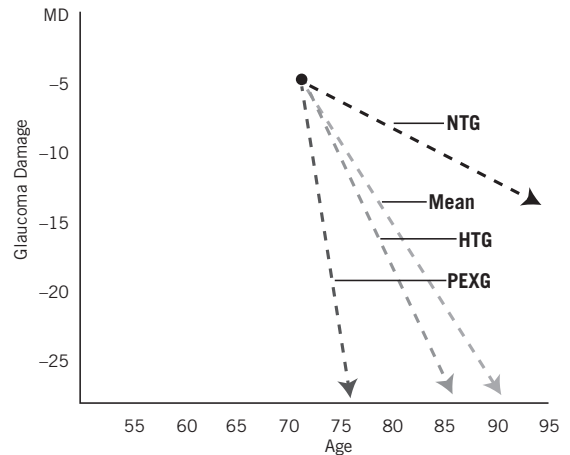
“Every 1 mmHg of IOP reduction was associated with a risk reduction of 10 to 13 percent, depending on the analysis.”

#### Disease progression is variable.

However, the most important consequence of the EMGT in Europe at the time, said Dr. Heijl, was the recognition that the rate of glaucoma progression is variable and difficult to predict, even in those being treated; and it is affected by such factors as age, initial eye pressure, and degree of glaucoma damage. An unexpected finding was that most patients will eventually progress to some extent, even if pressure is always normal. With this knowledge, Dr. Heijl said,

doctors must ask themselves, “Is this patient progressing at a speed that is of concern during his or her remaining lifetime, or is change occurring so slowly that it doesn’t matter?”

**Mean IOP, not fluctuation, is what matters.** In contrast to CIGTS and some other studies, the EMGT found that IOP fluctuation is not a risk factor when mean IOP was taken into account. “Clinically, this has made me less interested in diurnal tension curves,” Dr. Heijl said.



Rates of VF decline from the baseline mean deviation of  $-4$  dB seen in untreated patients with normal-tension glaucoma (NTG), high-tension glaucoma (HTG) and pseudoexfoliative glaucoma (PEXG) in the EMGT.

### LESSONS FOR CLINICIANS

#### Follow progression closely; reset target as needed.

“Because we are poor at guessing which patients will progress rapidly,” said Dr. Heijl, his protocol involves measuring IOP and testing visual fields every four months beginning at diagnosis. After two years, he takes a closer look at the rate of progression to see if the target pressure should be reset.

“It’s beneficial to lower pressure in patients progressing quickly, even if IOP levels have been in the range of 15 to 18 mmHg,” he said. “Some patients become considerably more stable with pressures in the 10- to 12-mmHg range.”

**Persist in eking out the extra mmHg.** Dr. Heijl said that the magnitude of treatment effect seen in the study has made him more persistent in striving for a few extra millimeters of pressure lowering, as long as the side effects remain manageable.

**Recognize the importance of exfoliation as a risk factor.** EMGT researchers found that exfoliation syndrome is an important pressure-independent risk factor for progression. For example, in a follow-up study of patients with ocular hypertension, exfoliation nearly doubled the risk of developing field loss more than nine years later.<sup>5</sup> “This high risk of conversion has made me consider treating these patients even in the absence of any signs of damage at all,” said Dr. Heijl.

### EMGT AT A GLANCE

- Seven to 11 years of follow-up
- 255 patients, aged 50 to 80, with early-stage glaucoma in at least one eye
- Entry criteria: median visual field mean deviation of  $-4$  dB and median IOP of 20 mmHg
- Randomized to initial treatment with a selective beta-blocker and ALT or left untreated until signs of progression appeared
- Main outcome measure: visual fields or optic disc photographs<sup>4</sup>

# Collaborative Normal-Tension Glaucoma Study

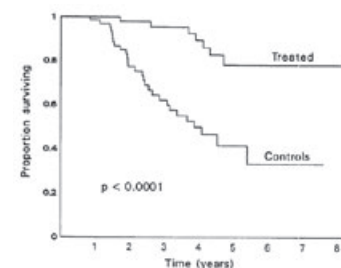
## IOP REDUCTION IMPORTANT EVEN FOR NORMOTENSIVES

### KEY FINDINGS

**IOP plays a role in NTG.** A major finding of the CNTG study was that glaucoma progression was slower in the treated group than in the untreated group. This answered the primary question of the trial: Is IOP involved in normal-tension glaucoma?

Although the role of pressure is now taken for granted, when the trial began, physicians were evenly divided about the pathogenesis of the disease, said Dr. Anderson, a CNTG investigator. Some thought it a waste of time to treat with pressure-lowering therapies. Others were treating it, but doing so halfheartedly because of the uncertainty about the benefit. “The study showed that it is worthwhile to treat NTG and move pressure from the high-normal to low-normal range, but you must be vigorous because it’s more difficult to lower pressure substantially when it’s already reasonably low,” he said.

**Cataract confounders.** In the CNTG study, patients who had filtering surgery were more likely than the other patient groups to develop cataracts. And because changes in visual field thresholds—a main outcome measure—are affected by cataract, corrections were needed to fully uncover the benefit of IOP lowering, said Dr. Anderson.



*Survival curves demonstrate the benefit of IOP-lowering treatment for NTG.*

Compared with EMGT, CNTG’s less-compelling results in the intent-to-treat analysis were likely due to this cataract effect, said Dr. Heijl. What many people missed in comparing results of the two studies, added Dr. Anderson, was that the criteria used in the EMGT trial automatically removed the cataract effect. “Also, EMGT didn’t have any patients who underwent surgery.”

**Natural history on display.** “An interesting aspect of the CNTG,” said Dr. Gedde, “is that it provided a unique opportunity to study the natural history of untreated NTG. Some patients who were enrolled in the study were never randomized, and others were randomized to the observation arm.”

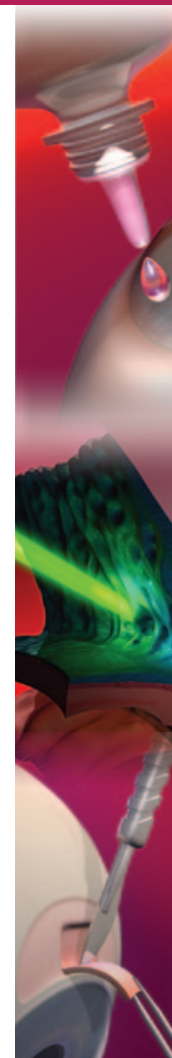
### LESSONS FOR CLINICIANS

**Distinguish between progressive and nonprogressive disease.** Progression in untreated NTG was highly variable, with a few patients deteriorating very rapidly without treatment and others at a moderate rate; but more than half did not have any demonstrable progression in five to seven years. This suggests that nonprogressive cases of NTG may exist, said Dr. Anderson. Therefore, the physician might choose to simply monitor a mild case of NTG, delaying treatment until it is shown to be progressive. “Or, if you have started treatment but are now contemplating more aggressive treatment with greater risk, you might pause and remember that half don’t require it.”

The obvious challenge, however, is identifying which patients have the progressive form of the disease, said Dr. Gedde. “For those with severe disease, you can’t really afford to wait to see if it will get worse because any increment of progression may be visually significant.”

**Surgery may not be necessary.** In CNTG, the goal was to lower pressure by 30 percent. The investigators were surprised that they were able to attain that goal in about half of the patients without surgery, using only laser and medical therapy (pilocarpine and systemic carbonic anhydrase inhibitors). With the medications available today, that pressure-lowering goal might be achieved without surgery in as many as 75 to 80 percent, said Dr. Anderson.

**Double-check potential progression.** Today, researchers continue to explore various protocols for assessing progression, but no clear standard has emerged. In this study, the investigators performed frequent visual field tests to monitor for subtle changes. Because visual field testing is subjective, especially with small increments of change, it is important to differentiate between testing variability and actual progression. They found that as many as five or six visual field confirmations were needed to avoid overdiagnosing decline.



### CNTG AT A GLANCE

- Five or more years of follow-up
- 260 patients with normal-tension glaucoma (NTG)
- Entry criteria: eyes with either progressive NTG or NTG with field defects impinging on the point of fixation
- Randomized to receive no therapy or IOP lowering by 30 percent with medication (pilocarpine or carbonic anhydrase inhibitor), laser, filtering surgery or a combination
- Main outcome measure: change from a three-field baseline in five of six follow-up visual fields<sup>6</sup>

# Advanced Glaucoma Intervention Study

## EFFECT OF SEQUENCE IN SURGICAL PROCEDURES

### KEY FINDINGS

**Reducing IOP slows visual field loss.** One of the first studies to show that a lower mean IOP results in a reduced risk of visual field progression, AGIS examined the long-term outcomes of two different surgical sequences for treatment of advanced glaucoma: ALT-trabeculectomy-trabeculectomy (ATT) versus trabeculectomy-ALT-trabeculectomy (TAT). Second and third procedures were performed as needed.

Patients with “advanced glaucoma” were defined as those with visual field loss at enrollment who

failed to achieve adequate IOP reduction despite use of maximum effective, accepted and tolerated medications.

Although not all patients had advanced glaucoma, most had an IOP of 18 mmHg or higher. Overall, the patients did fairly well in the long run.

**Many patients achieved stability.** “If you look at the rates of visual field loss or central vi-

sual loss as defined in AGIS,” said Kouros Nouri-Mahdavi, MD, assistant professor of ophthalmology at the Jules Stein Eye Institute in Los Angeles,

“nearly two-thirds of patients remained stable. In advanced glaucoma, I would consider this a reasonable outcome.”

**Race affected outcomes.** AGIS enrolled a large number of African-American patients (57 percent of the study population). The outcomes were different between the two surgical sequences depending upon whether the patients were African-American or Caucasian, said Dr. Nouri-Mahdavi, who is a coauthor on post hoc studies using the AGIS database but was not a part of the original study.

An analysis of sustained decrease of visual acuity showed that Caucasians did slightly worse—and African-Americans did markedly worse—if they were randomized to TAT rather than ATT, said Dr. Nouri-Mahdavi. According to visual field outcomes, Caucasians assigned to the ATT group fared better, while a worse outcome was again demonstrated for African-Americans.

### LESSONS FOR CLINICIANS

**Take race into account when choosing therapy.** Dr. Nouri-Mahdavi thinks that these differences are too frequently ignored. One of the lessons of AGIS is that “we should probably think more about tailoring our surgical approach according to ethnicity. For example, with some exceptions, my first surgical option in African-American patients would be laser trabeculoplasty,” he said.

Although some observers consider the results of AGIS less relevant now because of subsequent changes in surgical technique, Dr. Nouri-Mahdavi believes there is no proof that later developments—such as selective laser trabeculoplasty (SLT) and use of antimetabolites—have significantly altered outcomes of glaucoma in African-Americans compared to the time of the trial.

### AGIS AT A GLANCE

- Eight to 11 years of follow-up
- 591 patients (789 eyes), aged 35 to 80 at enrollment, with advanced POAG
- Entry criteria: patient on maximum tolerated medical therapy, baseline VA score 56 or better in the study eye, baseline AGIS visual field score of 1 to 16
- Randomized to receive ALT-trabeculectomy-trabeculectomy (ATT) or trabeculectomy-ALT-trabeculectomy (TAT)
- Main outcome measures: sustained decrease of visual field and sustained decrease of visual acuity<sup>7</sup>

## REFERENCES

- 1 Kass MA et al. *Arch Ophthalmol*. 2002;120(6):701-713.
- 2 Musch DC et al. *Ophthalmology*. 1999;106(4):653-662.
- 3 Lichter PR et al. *Ophthalmology*. 2001;108(11):1943-1953.
- 4 Heijl A et al. *Arch Ophthalmol*. 2002;120(10):1268-1279.
- 5 Grodum K et al. *Ophthalmology*. 2005;112(3):386-390.
- 6 Anderson DR. *Curr Opin Ophthalmol*. 2003;14(2):86-90.
- 7 The Advanced Glaucoma Intervention Study (AGIS). *Control Clin Trials*. 1994;15(4):299-325.
- 8 Gedde SJ et al. *Am J Ophthalmol*. 2009;148(5):670-684.
- 9 Minkler DS et al. *Ophthalmology*. 2008;115(6):1089-1098.

## Meet the Experts



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# Tube vs. Trabeculectomy Study

## EXPANDING THE USE OF SHUNTS

### KEY FINDINGS

**Trab vs. shunt: no clear winner.** The TVT study challenged the traditional paradigm of glaucoma surgical management in which tube shunts were reserved for high-risk eyes, said Dr. Gedde, a co-chairman of the study.

Indeed, the TVT results support expanding the use of tube shunts beyond patients with refractory glaucoma to those at lower risk of surgical failure than are typically treated with this procedure. They also demonstrate that low levels of IOP can be achieved with tube shunts in this patient group.

After three months, both procedures produced sustained pressure reduction to the low teens throughout the five-year duration of the study. In addition, rates of visual loss and of late or serious postoperative complications were similar between the two treatment groups.

**Subtle differences.** TVT did uncover some differences between the two procedures, however. Comparing the two, tube shunt surgery had a higher long-term success rate (cumulative probability of failure at five years was 47 percent in the trabeculectomy group and 30 percent in the tube group). In addition, the shunts had a lower rate of early postoperative complications and of reoperation for glaucoma.

In contrast, trabeculectomy plus MMC achieved better early pressure control (first three months) and less use of adjunctive medical therapy (first two years only).<sup>8</sup>

**Complications and failure rates.** The trabeculectomy complication rates in the TVT study were remarkably consistent with other prospective, randomized clinical trials such as CIGTS and AGIS, said Dr. Gedde. A systematic review of the literature in an Academy *Ophthalmic Technology Assess-*

*ment*<sup>9</sup> found that both trabeculectomy and tube failure rates were about 10 percent per year. The rate of trabeculectomy failure in the TVT study was consistent with this estimate; however, the tube shunt failure rate was approximately 5 percent per year, about half that seen in other studies.

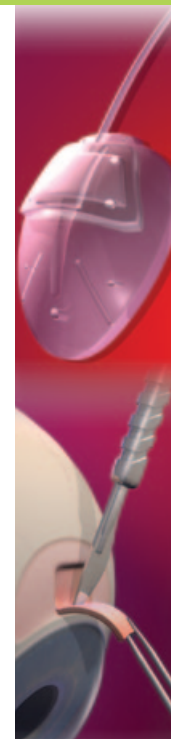
This better success rate for tube shunts in the TVT was largely related to the atypical population enrolled in the study, said Dr. Gedde. “We excluded refractory types of glaucoma, such as neovascular glaucoma, which are often included in other studies reporting outcomes of tube shunt surgery. We also recruited patients at lower risk of surgical failure than have historically had tube shunt implantation, such as patients with only prior clear cornea cataract surgery.”

### LESSONS FOR CLINICIANS

#### Put tubes in your armamentarium.

Dr. Nouri-Mahdavi called the data reassuring. “TVT makes me feel more comfortable placing drainage shunts in cases where I previously would have been more likely to do a trab as the first approach,” he said.

**Assess the patient’s unique needs.** Factors such as tolerance of medical therapy or willingness to undergo repeat glaucoma surgery, if needed, must be considered when choosing between the two procedures, said Dr. Gedde. In addition, the surgeon’s experience and skill with each of the procedures are important considerations.



### TVT AT A GLANCE

- Five years of follow-up
- 212 patients, 18 to 85 years of age
- Entry criteria: prior cataract or glaucoma filtering surgery and uncontrolled glaucoma with IOP of 18 mmHg to 40 mmHg on maximum tolerated medical therapy
- Randomized to receive either tube shunt surgery and/or trabeculectomy with mitomycin C (MMC)
- Main outcome measures: IOP, visual acuity, visual fields, surgical complications, glaucoma medications and treatment failure<sup>8</sup>

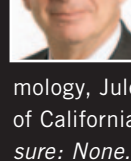


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