Welcome to the “Landmark Studies” column. Landmark studies are the building blocks of evidence-based glaucoma care. If you do not know this information, learn it. If you forgot it, relearn it. This series begins with the all-important and multifaceted Ocular Hypertension Treatment Study (OHTS). Dr. Kass, lead investigator for the study, was gracious enough to respond to 11 of my questions highlighted in red. Try to answer the questions before you read his responses. It is a great way to learn! I am reminded of a phrase from one of my mentors, George L. Spaeth, MD, who during glaucoma rounds would deftly turn to the unwitting fellow and say, “Quiz time!” His or her heart rate would increase, and an efficient learning mode ensued. So, let’s start with a quiz. After reading the article, ask yourself the questions again and see if your answers are better. The next column will cover the wealth of visual field data related to the OHTS by Chris Johnson, PhD, and colleagues, luminaries in their field.

—Section Editor Ronald L. Fellman, MD

WHAT QUESTION WAS THE OCULAR HYPERTENSION TREATMENT STUDY DESIGNED TO ANSWER?

The OHTS had two major goals. The first was to determine the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the onset of primary open-angle glaucoma (POAG) in ocular hypertensive subjects. In other words, does treatment prevent POAG? The second goal was to determine which baseline demographic and clinical features are predictive that an ocular hypertensive person will go on to develop POAG. In other words, which ocular hypertensive patients are at high risk, and which are at low risk of developing POAG? When these first two questions had been answered, we added a third major goal. It was to determine if there is a penalty for delaying the treatment of ocular hypertension (OHT). In other words, does it matter when treatment is started in ocular hypertensive patients?

WHAT WERE THE KEY HISTORICAL FACTORS THAT PROMPTED YOUR TEAM TO CARRY OUT THE OHTS?

The medical treatment of glaucoma dates back to the 19th century. Ophthalmologists had essentially universally accepted the concept that lowering IOP by medical means was therapeutic for glaucoma long before randomized clinical trials became the gold standard for judging clinical efficacy. Beginning in the 1970s and 1980s, a number of health economists, managed care organizations, and some ophthalmologists became concerned about the lack of scientific evidence supporting this approach to glaucoma. David M. Eddy, MD, PhD, stated that Medicare (and perhaps, by extension, health insurance companies) should not pay for clinicians to screen, examine, test, or treat patients with glaucoma until there was stronger scientific evidence that treatment was effective. Prior to OHTS, there were several published studies and a meta-analysis on the question of whether early treatment was helpful in reducing the incidence of POAG in ocular hypertensive patients. Unfortunately, these studies had conflicting results. We decided to answer this question once and for all by designing the OHTS.

HOW WAS THE STUDY DESIGNED TO ANSWER THE QUESTION?

The design of the OHTS was a classic randomized clinical trial. We randomized 1,636 ocular hypertensive patients to either observation or treatment with any commercially approved topical ocular hypotensive medication available in the United States. Of these participants, 819 were randomized to the observation group, and 817 were randomized to the treatment group. The
goal of treatment was to lower IOP by 20% or more and to reach a pressure of 24 mm Hg or less.

At the study entry, the patients were 40 to 80 years of age and had an IOP of 24 to 32 mm Hg in one eye and 21 to 32 mm Hg in the fellow eye. The participants could have no glaucomatous damage on standard clinical tests—full-threshold, white-on-white 30-2 Humphrey visual field tests (Carl Zeiss Meditec, Inc., Dublin, CA), and stereoscopic optic disc photographs. The patients were examined twice a year, which is when visual fields were performed. Stereoscopic optic disc photographs were taken once a year. Masked readers reviewed the visual fields and photographs in reading centers. If a participant had two consecutive sets of stereo optic disc photographs that showed a deterioration from baseline or three consecutive sets of reliable visual fields that were abnormal, with the abnormality in the same location and on the same index, the participant reached an endpoint. The clinical information was then reviewed by the endpoint committee, which decided whether the change was due to POAG or another condition.

In the second phase of OHTS, we posed another question: does delaying the treatment of OHT matter? In order to find an answer, we offered treatment to the original observation group after a mean of 7.5 years without medical treatment while continuing treatment in the original medication group. This strategy created an early-treatment group (treated for a mean of 13 years) and a delayed-treatment group (observed for a mean of 7.5 years and then treated for a mean of 5.5 years). We then compared the cumulative occurrence of POAG in both groups.

WHAT WERE THE MOST SURPRISING FINDINGS FROM THE OHTS?

The most surprising finding in OHTS was that central corneal thickness (CCT) is a powerful predictive factor for developing POAG. The question is why participants with thin corneas are at a higher risk of developing POAG while participants with thick corneas are at a lower risk. The simplest answer would be that the thickness of the cornea affects the measurement of IOP. However, the magnitude of the effect of corneal thickness on the risk of developing POAG seems to be too great to be explained by a misreading of IOP. It is possible that corneal thickness is related to other structural properties of the eye that influence susceptibility to POAG.

Another surprising finding was that two abnormal visual fields in a row are not sufficient to diagnose the onset of glaucomatous visual field loss. During the planning phase of OHTS, we thought that, if a participant had normal and reliable visual field tests to qualify for the study and then, at a later time, had two abnormal and reliable visual fields in a row, the patient surely had developed POAG. We observed that, even after two abnormal visual fields in a row, the next visual field was normal 40% of the time. We were very surprised by this finding, and the Data and Safety Monitoring Committee changed the endpoint criteria to three reliable and abnormal fields in a row. This finding was unexpected since the OHTS employed a high level of feedback and quality control for the visual field technicians. In many ways, we had optimized visual field testing in a clinical trial, but three consecutive abnormal visual fields were still needed to reach a clear POAG endpoint.

The third surprising finding was that medical treatment was as effective in African Americans as those classified as “others.” Within each stratum of risk, African Americans and others had similar reductions in IOP and a similar decrease in the incidence of POAG.

WHAT ARE THE MOST IMPORTANT CLINICAL TAKE-HOME MESSAGES FROM THE OHTS?

There are five important take-home messages for clinicians.

1. Topical ocular hypotensive treatment is safe and effective in reducing the incidence of glaucoma in ocular hypertensive subjects. Treatment produces roughly a 50% decrease in the incidence of glaucoma.

2. Although the 50% reduction in the incidence of glaucoma occurs across the risk spectrum of ocular hypertensive participants, the absolute reduction is greatest in the high-risk participants. This means that high-risk patients should be observed more carefully and may benefit from early treatment. Conversely, patients at low risk may not need such frequent follow-up and probably do not need early treatment in most cases. The decision to treat ocular hypertensive patients can be based on their risk of developing POAG, taking into consideration the patient’s age, health status, life expectancy, and personal preference.

3. Baseline age, IOP, CCT, vertical cup-to-disc ratio, and pattern standard deviation do a good job of stratifying the level of risk in ocular hypertensive patients. These factors are all relatively easy to gather and do not require specialized equipment beyond what is normally in a clinician’s office. This five-factor model has proven to be very useful and was confirmed in the participants of the European Glaucoma Prevention Study. It was often said that patients with OHT develop POAG at a
rate of about 1% per year. It is possible to identify groups of ocular hypertensive patients whose 5-year risk of developing POAG is less than 5% but also groups whose 5-year risk is 35% or higher.

4. Delaying treatment for a mean of 7.5 years has a relatively small absolute effect on the incidence of POAG in low-risk ocular hypertensive patients (reduced the 13-year incidence of POAG from 8% to 7%) but a much larger absolute effect in the high-risk group (reduced the 13-year incidence of POAG from 40% to 28%).

5. Although the treatment of OHT is protective in African Americans, they still had a higher incidence of POAG than the participants classified as other in OHTS. On the basis of thinner baseline CCT and larger baseline cup-to-disc ratio, African Americans as a group are at higher risk for developing POAG. In other words, African Americans are overrepresented in the high-risk group and underrepresented in the low-risk group.

THE OHTS CLEARLY DELINEATED RISK FACTORS. SHOULD PHYSICIANS BE USING A RISK CALCULATOR ON A DAILY BASIS FOR OCULAR HYPERTENSIVE PATIENTS? IF SO, WHAT IS THE BEST WAY TO ACCOMPLISH THAT?

The risk calculator is useful for predicting the chances that an ocular hypertensive patient will develop POAG over 5 to 10 years. As stated previously, the baseline factors used are age, IOP, CCT, vertical cup-to-disc ratio, and pattern standard deviation. It is not necessary to use a risk calculator in all patients. Many clinicians take these factors into consideration when evaluating patients without formally calculating the risk. On the other hand, some patients may benefit from such a calculation. A handheld calculator is available, or the physician can go online to the OHTS Web site (www.ohts.wustl.edu/risk). The risk calculator will be more accurate in patients who resemble the participants in OHTS.

CONSIDERING THE INFORMATION GATHERED REGARDING VISUAL FIELDS, 40,000 OF THEM, WHAT IS THE BEST CLINICAL RECOMMENDATION REGARDING VISUAL FIELDS IN OCULAR HYPERTENSIVE PATIENTS. IS IT THREE VISUAL FIELDS BEFORE CONFIRMING DEFECTS?

The OHTS initially used full-threshold, white-on-white 30-2 Humphrey visual fields. Later, we utilized the Swedish interactive thresholding algorithm strategy, which appeared to function well. I suspect that many clinicians prefer the 24-2 pattern to the 30-2 pattern, but that was not formally evaluated in OHTS. The early diagnosis of glaucomatous visual field loss requires three consecutive visual fields. The OHTS did not evaluate other forms of perimetry such as blue-on-yellow or frequency doubling.

WHAT DID THE OHTS TELL US ABOUT THE SIGNIFICANCE OF A DISC HEMORRHAGE?

The occurrence of an optic disc hemorrhage increases the risk of developing POAG approximately sixfold. However, not all ocular hypertensive patients who develop an optic disc hemorrhage go on to develop glaucoma. We followed 128 eyes that had an optic disc hemorrhage before being diagnosed with POAG, and only 17 (13%) of them went on to develop POAG over the subsequent 2.5 years. Thus, an optic disc hemorrhage is clearly a risk factor for developing POAG, but it is not synonymous with developing POAG.

BASED ON THE OHTS, SHOULD WE TELL PATIENTS WHO ARE STARTING DROPS THAT THEY ARE MORE PRONE TO DEVELOP A CATARACT?

In the first phase of OHTS, we found a slight excess of cataract surgery in the treatment group (7.6% over a mean of 6.3 years) as opposed to the observation group (5.6% over a mean of 6.3 years). However, we could not find a difference between the medication and observation groups on a number of measures, including visual acuity, foveal sensitivity, and refraction as well as formal assessment of lenticular opacification, except for a slight increase in posterior subcapsular opacity in the medication group. Thus, we did not find evidence of a general effect of topical medication on lenticular opacification. It is possible that a subset of patients is affected by the medication or the preservatives. Further study is needed.

CAN YOU CLEAR UP THE CONTROVERSY SURROUNDING DIABETES MELLITUS AS A RISK FACTOR FOR CONVERSION TO POAG?

The short answer is no. The literature on diabetes mellitus and the development of POAG is complex and contradictory. There are studies showing that diabetes increases the risk, decreases the risk, and does not change the risk of developing POAG. In the initial analysis of OHTS, diabetes appeared to have a protective effect against the development of POAG. However, in detailed reanalysis of the data, we were unable to confirm this finding. At this point, I would say that the relationship between diabetes mellitus and glaucoma remains unclear, and OHTS does not provide a definitive answer to this question.
WHAT ARE THE MOST IMPORTANT LESSONS FROM THE OHTS REGARDING THE NATURAL HISTORY OF OHT?

Patients with OHT continued to develop POAG throughout study follow-up. There was no time after which the conversion to POAG ceased.\(^4\) Over the course of the OHTS, participants seemed to divide into those who were destined to develop POAG and those who were stable over the course of follow-up. The former had slightly worse visual field indices at baseline, and the slopes of these functions worsened over time.\(^4\) This suggests a prolonged prodrome before glaucomatous damage is detected and confirmed by conventional clinical measures. In contrast, the remaining patients had a stable mean defect and pattern standard deviation over a mean of 13 years.\(^4\)

The OHTS was supported by grants EY09341 and EY09307 from the National Eye Institute and the National Center on Minority Health and Health Disparities, National Institutes of Health, Bethesda, Maryland; an unrestricted grant from Research to Prevent Blindness, New York, New York; Merck Research Laboratories, Whitehouse Station, New Jersey; and Pfizer, Inc., Peapack, New Jersey.

Section Editor Ronald L. Fellman, MD, is a glaucoma specialist at Glaucoma Associates of Texas in Dallas and clinical associate professor emeritus in the Department of Ophthalmology at UT Southwestern Medical Center in Dallas. Dr. Fellman may be reached at (214) 360-0000; rfellman@glaucomaassociates.com.

Michael A. Kass, MD, is a professor and chair­man of the Department of Ophthalmology and Visual Sciences at Washington University School of Medicine in St. Louis, Missouri. He is the lead investigator of the OHTS. Dr. Kass may be reached at (314) 362-3937; kass@vision.wustl.edu.