

The Canadian Glaucoma Study

This multicenter, prospective, longitudinal trial identified a unique systemic risk factor for the progression of primary open-angle glaucoma.

BY BALWANTRAY C. CHAUHAN, PhD

The landmark randomized clinical trials in glaucoma that included untreated arms confirmed the potency of IOP as a risk factor across the disease's spectrum.¹⁻³ They also showed that lowering IOP reduces the incidence of glaucoma and its progression. Because decreasing IOP does not always prevent glaucomatous progression, however, many clinicians and scientists believe that factors in addition to or independent of IOP may play a role in progressive visual field loss.

In 1990, Schulzer et al found that patients with peripheral vasospasm had glaucomatous visual field damage proportional to their highest recorded IOP.⁴ A corollary hypothesis stated that vasospastic patients might benefit more from ocular hypotensive treatment than nonvasospastic patients. The multicentered, interventional Canadian Glaucoma Study (CGS) was designed to investigate this hypothesis by measuring the predictive value of a series of candidate baseline risk factors for glaucomatous visual field progression. They included susceptibility to peripheral vasospasm and hematological, coagulative, and immunopathological variables.^{5,6} This article describes the baseline characteristics and preliminary results of the CGS.

THE STUDY'S DESIGN

Researchers began designing the CGS in 1992. They recruited and tested the first patient in 2004 and evaluated the last patient in 2005. A total of 258 patients were

recruited from five university-based eye care centers across Canada. After baseline testing, patients were followed every 4 months with standard automated perimetry, short-wavelength automated perimetry, and optic disc imaging with confocal scanning laser tomography. Conventional disc photographs were also obtained at less frequent intervals. Progression was defined by confirmed changes in the visual field with standard automated perimetry.

During the study, the patients' IOPs were maintained with a standardized protocol that ranged from monotherapy to trabeculectomy. According to the study's design, newly diagnosed patients were mandated to have a 30% reduction in IOP. Previously diagnosed patients who developed progressive visual field loss during the study (as measured by a change from baseline standard automated perimetry) had an additional 20% reduction in IOP from their original physician-defined target by moving to the next step in the treatment protocol. Patients were followed for a median of 5.3 years, with 65% of patients completing at least 5 years and 26% at least 7 years of follow-up.

MAIN OUTCOMES

At baseline, female subjects had a threefold higher prevalence of thyroid disease and a twofold higher prevalence of migraine than male subjects.^{5,6} In addition, almost 2.5 times more women had diabetes compared with men. The CGS found four variables to be independently predictive of glaucomatous visual field progression (Table 1).

Only IOP values before the glaucomatous progression (if it occurred) were included in the analysis. Although the distribution of IOPs on follow-up was narrow (50% of the patients had mean measurements of

TABLE 1. HAZARD RATIOS FROM THE COX PROPORTIONAL HAZARDS ANALYSIS

Risk factor	Hazard Ratio	Confidence Interval
Abnormal baseline anticardiolipin antibody	3.86	1.60 to 9.31
Higher baseline age (per year)	1.04	1.01 to 1.07
Higher mean follow-up IOP (mm Hg)	1.19	1.05 to 1.36
Female gender	1.94	1.09 to 3.46

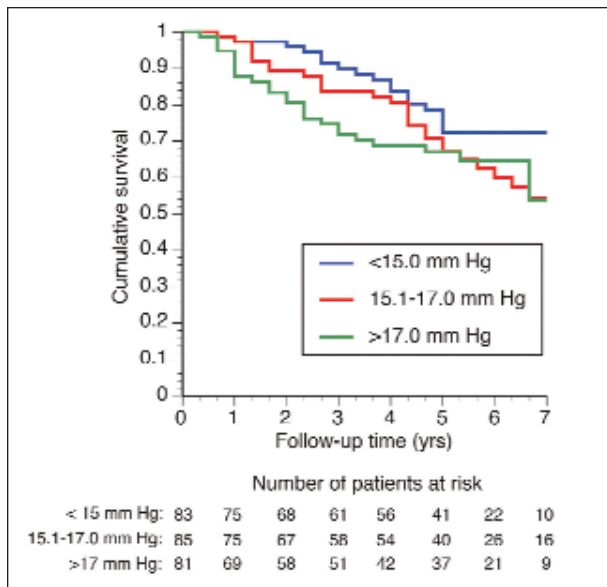


Figure 1. Cumulative survival of patients divided into equal thirds based on mean IOP at follow-up.

between 15.5 and 17.0 mm Hg), IOP still appeared to be a significant risk factor for progression (Figure 1). Of importance, after controlling for all confounding factors, women were twice as likely to progress compared to men.

Vasospastic patients had a lower rate of glaucomatous progression than nonvasospastic participants, but the difference was not statistically significant. There were more than 1.5 times as many vasospastic women than men, and, interestingly, the tendency of vasospastic patients to have a better outcome under treatment persisted when the data were stratified by gender (Figure 2).

TAKE-HOME POINTS

The CGS adds to the number of populational studies that confirm the beneficial effects of reducing IOP in glaucoma patients. The CGS, like the Collaborative Normal Tension Glaucoma Study¹ but not the Early Manifest Glaucoma Trial,² found that female gender was a powerful risk factor for progression. Geographical diversity and the interplay among genetic and environmental factors, among others, may be at the root of these differences.

The CGS identified a novel risk factor—a positive anticardiolipin antibody test—for glaucomatous progression. Patients with a positive test result were almost four times as likely to experience disease progression compared with those with a negative result. Why this test was highly significant is unclear. It is important to note that only a small minority of patients tested positive for anticardiolipin antibodies. This test is therefore not recommended for routine use in glaucoma patients. Nonetheless, the find-

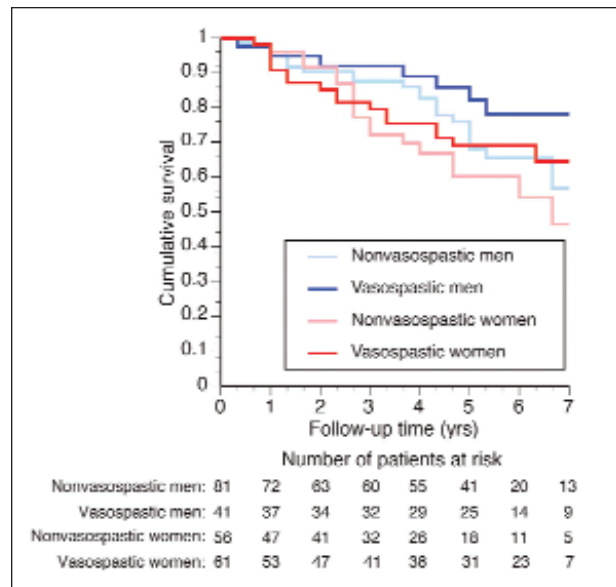


Figure 2. Cumulative survival of nonvasospastic and vasospastic patients stratified by gender.

ings of the CGS are quite powerful and indicate a need for further research into the types of glaucoma associated with the presence of anticardiolipin antibodies. Although the CGS could not statistically confirm that treated vasospastic patients had a better outcome than nonvasospastic patients, the investigators observed such a trend. It is possible that the effect of vasospasm on glaucomatous progression is smaller than that predicted by the study's design and sample size. Further work on several aspects of the CGS is underway for future reports. □

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