control group as reported in the result section ($n = 38$ and 62, respectively) to the number depicted in Table 2 ($n = 41$ and 59, respectively).

The potentially important finding that a negative association (although statistically insignificant) between CCT and HRT II optic disc area in glaucoma patients should be carefully considered. This is in line with several previous reports that also described a statistically insignificant negative association between CCT and HRT optic nerve head structural parameters in glaucomatous eyes. However, the interpretation of the borderline negative correlation in the control group remains problematic as the heterogeneous control group of healthy and glaucoma-suspect eyes limits its application.

In conclusion, although we believe that the study of Insull *et al*. is of potential interest for glaucoma research, the results should be interpreted with caution because of the potential limitations.

Mohammadali M. Shoja MD, Alon Harris PhD, Yochai Z. Shoshani MD and Brent Siesky PhD
Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, Indiana, USA
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Optic disc area and correlation with central corneal thickness, corneal hysteresis and ocular pulse amplitude in glaucoma patients and controls: response

We thank Shoja *et al*.[1] for their interest in our paper.[2] We agree that the results from our study need to be interpreted cautiously because of the relatively small sample size, incomplete dataset and research methodology.

In 2007, Pakravan *et al*. reported on 72 eyes with primary open-angle glaucoma, and found a statistically significant inverse correlation between central corneal thickness and optic disc area ($r = -0.28$, $P = 0.036$).[3] As we had some data on the central corneal thickness and optic disc area, we wanted to make our results available to those interested in this research area. Our study had the additional advantages of having a control group of patients without glaucomatous optic neuropathy, as well as data on corneal hysteresis and ocular pulse amplitude.

Based on our results, we can only conclude that there is an overall negative correlation between central corneal thickness and optic disc area. However, this is not statistically significant when evaluated separately for the glaucoma and control groups. We concur that the statistical significance observed for the combined glaucoma and control group may be due to the increased sample size. Although we are unable to make any firm conclusions from our results, nevertheless we feel that our study does contribute to the growing literature on this subject.

Ghee Soon Ang MRCOphth, Simon Nicholas FRANZCO and Anthony Wells FRANZCO
Capital Eye Specialists, Wellington, New Zealand
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Bevacizumab: not as good with more adverse reactions? Response

Beaumont addresses both the relative safety and efficacy of bevacizumab and ranibizumab as described in our recent article on the 1-year results of the comparison of age-related macular degeneration treatments trials (CATT).[1] The initial premise stated by Beaumont is that ophthalmologists 'have a vested interest in proving what they have been doing is safe and effective' and therefore, statements made in our paper 'should be carefully scrutinized'. Certainly, critical non-biased review of our data is welcome. But the suggestion that there is a bias in the conduct or reporting of our study is groundless and reveals a lack of understanding as to the study history and structure. CATT is an independent group of investigators. The study officers have no conflict of interest, and many of the ophthalmologists in CATT are in fact primarily ranibizumab users. The

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Center for Medicare and Medicaid Services had no input into the design or conduct of our study. All primary outcome and most secondary measures were masked assessments. External review of our masking suggests that it was robust. All results and drafts of the manuscript were exhaustively reviewed by an independent Data and Safety Monitoring Committee who approved the final manuscript before submission. CATT employed every measure available to ensure that the data and their interpretation were as free from bias as possible. We will first address safety concerns raised by Beaumont and then efficacy.

When CATT was initiated, arterial thromboembolic events (heart attacks, strokes and deaths from vascular causes) had been associated with systemic administration of anti-vascular endothelial growth factor (anti-VEGF) agents for treatment of cancer. Questions had also been raised about an increased risk of stroke with intraocular injection of ranibizumab. Reliable detection (≥80% power) of even a doubling of risk between drugs for relatively rare events (~2%) requires a sample size that is at least twice the 1200 patients enrolled in CATT. In the 1-year CATT results, there was no difference in rates of arterial thromboembolic events between drugs with 2.2% (13 of 599) occurring in the ranibizumab group and 2.4% (14 of 586) in the bevacizumab group ($P = 0.83$).

Since the initiation of CATT, many conditions have been linked to drugs that suppress VEGF when delivered systemically.[2] Beaumont highlighted venous thromboembolic events and gastrointestinal bleeding and ulcers as examples of specific adverse events previously linked to anti-VEGF drugs that occurred approximately 1% more often in patients treated with bevacizumab. We cannot replicate Beaumont's figures; the *P*-values we calculate are in the range of $0.05 < P < 0.10$ rather than <0.001, as calculated by Beaumont. With many specific conditions to choose from, some imbalances are likely. Of note, there were more people with myocardial infarctions in the ranibizumab group (8/599 = 1.3%) than in the bevacizumab group (3/586 = 0.5%). Imbalances of this magnitude may signal excess risk in one group; however, more data are needed to determine whether these imbalances are spurious or real.

We reported in the abstract of the paper and commented in the discussion on the higher percentage of patients in the bevacizumab group (24.1%) than in the ranibizumab group (19.0%) who had serious adverse events, mainly hospitalizations, involving a wide array of conditions. Even after we excluded adverse events previously associated with VEGF suppression,[2] an imbalance in the proportion of people with a serious adverse event remains between bevacizumab (20.7%) and ranibizumab (16.9%; $P = 0.10$). The lack of specificity in the higher rates in the bevacizumab group suggests that despite randomized treatment assignment, the CATT patients treated with bevacizumab may be less healthy overall and more likely to develop adverse events of any kind. In addition, the finding of more adverse events in patients who received less drug (pro re nata (PRN) group) adds further credence to the possibility that the imbalance may be due to chance or a difference in baseline health status.

In summary, we believe that adverse events in CATT are presented and discussed accurately in our paper. We wish that we had more definitive data to either confirm any true excess risk or reassure all ophthalmologists and patients that there are no differences in the safety of the two drugs. However, we must await the data from the second year of follow-up of the CATT patients and the results from other clinical trials comparing ranibizumab and bevacizumab to provide clarification.

Regarding efficacy, CATT provides clear results on the equivalence of these drugs on visual acuity through 1 year. The graphical displays at time points during the first year of treatment show the ranibizumab groups and the bevacizumab groups with nearly identical results both when treatment was administered monthly and when treatment was administered PRN. Analyses of the mean change in visual acuity at 1 year, the primary outcome measure, show that differences of five or more letters between drugs can be ruled out with high statistical confidence. In addition, all other visual acuity metrics were virtually identical between drugs. Beaumont points out that 3% more patients in the ranibizumab monthly group gained ≥3 lines of vision and that this 3% might be an important consideration when choosing drugs. We note that this 3% was not statistically significant and that 3% more patients receiving bevacizumab PRN had a ≥3 line gain as compared with ranibizumab PRN, which is the most common way these drugs are administered. Further, the group that had the highest rate of ≥3 line gain at all other time points was bevacizumab monthly (data shown in Fig. 2C[1]). We believe this represents nothing more than random variation, and the data best support a conclusion of equivalence between drugs.

Anatomical differences were noted between treatment groups. Patients treated with ranibizumab, particularly those treated monthly, had less fluid in the retina and thinner mean retinal thickness than those treated with bevacizumab. However, the absolute difference in fluid was small, and there was no visual acuity correlate. There has been relatively little study of the prognostic value after anti-VEGF therapy of the anatomic features imaged on optical coherence tomography and fluorescein angiography. We do not know if these anatomic differences will have an impact on vision later on. The visual acuity measurements taken during the second year of follow-up will tell us if the equivalent effects of the two drugs persist beyond 1 year.

Relative to the treatments available 6 years ago, the results of PRN treatment with either drug are excellent. However, on average, CATT patients treated PRN gained two letters less than patients treated monthly. The proportion of PRN-treated patients with visual acuity 20/40 or better was 62% as compared with 67% of monthly treated patients. Treating PRN with monthly observation may result in slightly less gain in visual acuity; however, this must be weighed against the fact that PRN patients had four or five fewer injections during the first year than monthly treated patients. Some people may prefer monthly treatment to be sure to achieve the best possible vision, whereas others may welcome relief from the burden of monthly injections.

More data from the second year of CATT and the results from other clinical trials of ranibizumab and bevacizumab will help clarify questions concerning safety and the effects on vision of using less than monthly dosing for either drug.

Daniel F Martin MD,[1] Maureen G Maguire PhD[2] and Stuart L Fine MD[3]

[1]*Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio,* [2]*Department of Ophthalmology, University of Pennsylvania, Philadelphia, Pennsylvania, and* [3]*Department of Ophthalmology, University of Colorado Medical Center, Denver, Colarado, USA*

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