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Author reply

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Dear Editor

Krishnamurthy et al posed relevant questions regarding our study.¹ First, we do not agree that “this may not be a good design when the risk factor is systemic like MAP [mean arterial pressure].” The risk factor of primary interest is an independent (predictor) variable in the model and visual field progression is an eye-specific dependent variable (outcome). For an adequate assessment of confounders, other eye-specific predictors needed to be entered in the multivariable model, such as intraocular pressure (IOP) and central corneal thickness (CCT), among others (see our Table 2),¹ because they have consistently been shown to be significant risk factors for glaucoma progression. It is important to perform this type of analysis given that within a same patient there can exist substantial differences between eyes with regard to IOP and CCT, and one needs to take into account these and other eye-specific predictors in the model. These variables can also play a role in the outcome measure (progression in 1 eye), even when the risk factor of primary interest is a systemic one. Otherwise, one could mistakenly assume that the reason an eye progressed was low nocturnal MAP when in fact high IOP and decreased CCT could have played a more important role in that eye. The fact that IOP (or other eye-specific variables) was not a significant predictor of progression in our study does not mean that IOP was not a confounder. Moreover, these issues have been addressed similarly to other studies (e.g., Early Manifest Glaucoma Trial [EMGT], Ocular Hypertension Treatment Study [OHTS], Collaborative Normal-Tension Glaucoma Study [CNTGS]), in which eye-specific and

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patient-specific predictors (including blood pressure) were investigated as risk factors for progression in one or both eyes.

Regarding the second claim, a seemingly unrelated regression equations approach was employed to assess the relationship of predictors to the global progression rate primary outcome. This multivariate approach is appropriate since the outcome equation for each eye has eye-specific (left/right eye) explanatory variables. In this class of linear models, each eye has a coefficient for each explanatory variable. The hypothesis test for a particular explanatory variable assesses whether the corresponding coefficients for each eye are both equal to zero using a Wald test. It could happen that one eye has a regression coefficient significantly different from zero, but the other eye does not. In this case, the progressing eye may still conclude a significant effect. The R^2 for the left and right eye regression models are 31.8% and 45.8%, respectively. For each of the significant regression coefficients, we reported the previously stated Wald test P value as well as the 95% CI for the corresponding left and right eye regression coefficients. Taken together, the three 48-hour measures of blood pressure contrasting daytime mean blood pressure with blood pressure during sleep shows that the total time that the MAP during sleep is >10 mmHg below the daytime mean ($P = 0.02$, right eye 95% CI, 0.002–0.029; left eye 95% CI, 0.001–0.038) is a significant predictor of global progression. The area that represents the time multiplied by the magnitude of nocturnal blood pressure that were >10 mmHg below daytime MAP ($P = 0.03$, right eye 95% CI, –0.000–0.002; left eye 95% CI, 0.000–0.002) also predicted progression.

Finally, we did not suggest that nocturnal reductions should be eliminated, even in eyes with progressive glaucoma. Nocturnal falls of MAP are a physiologic event; issues arise when the pressure drop exceeds the capacity of autoregulatory mechanisms. With regard to the challenge “to assess the clinical significance of these results,” we would like to highlight that normal tension glaucoma patients with nocturnal MAP drops below 10 or 20 mmHg of daytime MAP are at risk of visual field progression. Clinicians should therefore consider this possibility when normal tension glaucoma patients continue to progress despite medical therapy, because this could be at least in part owing to these pressure drops. What the authors deem “difficult” is a different question that was not our purpose, that is, to test whether modifying nocturnal MAP decreases the risk of progression. This issue can only be addressed in a prospective, randomized, controlled trial. The knowledge of the “strength of associations and the proportion of variance explained by the models,” whether strong or weak, does not answer the authors’ question unless interventional studies that assess “causality”—such as randomized, controlled trial—are performed first.

References

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