Letter to the Editor:

Calcium channel blockers and risk of primary open-angle glaucoma


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To the Editor:

I read with interest the perspective by De Moraes and colleagues about the implications for glaucoma care of new systemic hypertension treatment recommendations.\textsuperscript{1} I congratulate the authors on a thorough assessment of the sometimes conflicting evidence. In particular, it was emphasized that there is growing evidence that the relationship between blood pressure (BP) and glaucoma is modified by the treatment of systemic hypertension. I would like to suggest an additional and related hypothesis. It might be that specific classes of antihypertensive medication are mediating an increased risk of glaucoma. In a large study of US insurance billing data, using calcium channel blockers was associated with a 26% increased risk of primary open-angle glaucoma (POAG; 95% CI 18%-35%; \(P=1.8\times10^{-11}\)).\textsuperscript{2} This was in contrast to other classes of antihypertensive. For example, the most commonly prescribed antihypertensive drug class in the study was angiotensin-converting-enzyme inhibitors (ACE inhibitors). Despite the large sample size, there was no significant association between ACE inhibitor use and POAG (OR 0.97; 95% CI 0.91-1.03; \(P=0.29\)).\textsuperscript{2} In addition to specifically implicating calcium channel blockers as potentially harmful for glaucoma, this study also suggests that the mechanism affecting glaucoma risk may be independent of BP-lowering, given that the association was not seen with other anti-hypertensive classes. Might it be that lower BP is simply a marker for calcium channel blocker use, but not the mechanism influencing glaucoma risk? Genetic studies can be helpful for assessing whether an observed association is causal or not.\textsuperscript{3} Aschard and colleagues examined the relationship between BP, IOP and POAG using genotypic data; they found no evident genetic correlation between BP and POAG which strongly contrasted with the high genetic correlation they observed, as expected, between IOP and POAG.\textsuperscript{4} This suggests that the observed phenotypic relationship between BP and POAG is not causal, and supports the hypothesis that the observed association is due to confounding by antihypertensive treatment.

On an unrelated note, I would also like to encourage readers to interpret studies reporting ocular perfusion pressure (OPP; BP minus IOP) surrogates very cautiously. It is impossible to untangle the individual effects of IOP and BP from so-called OPP.\textsuperscript{5-7} Any crude association observed between OPP and glaucoma may be related solely to the IOP component, given the known strength of IOP as a risk factor for glaucoma.\textsuperscript{8} This has led investigators to adjust OPP for IOP in multivariable regression models. However, this will inevitably result in the situation that the coefficients for OPP actually represent the effect of BP only, and not OPP. This has been substantiated mathematically and also clearly demonstrated using a simulated dataset.\textsuperscript{5} Future research in the field should avoid OPP surrogates. The clearest way to examine the differential effects of BP and IOP on glaucoma risk is to examine both terms separately (not one subtracted from the other), firstly crudely, and then in the
same multivariable model. Clearly, given the emerging evidence, stratifying analyses by antihypertensive treatment status is important.

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References:


