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Re: Maggio et al.: Vitreomacular adhesion and the risk of neovascular age-related macular degeneration (*Ophthalmology*. 2017;124:657-666)

TO THE EDITOR: We have read with interest the publication of Maggio et al, wherein they report no relationship between the state of the vitreomacular interface and the risk of neovascular age-related macular degeneration (AMD). This finding is in contrast with multiple previous studies, which found that the presence of a posterior vitreous detachment (PVD) was associated with dry AMD, whereas vitreomacular adhesion is a risk factor for exudative AMD.[1–3] Studies have also found that vitreomacular adhesion hampers therapy with anti-vascular endothelial growth factor injections, necessitating more injections with poorer results.[4,5] One possible explanation for this incongruity is that this most recent study only used OCT to evaluate the state of the vitreous, and not ultrasound imaging, as previous studies have used. Indeed, in past studies ultrasound imaging was critical for accurately diagnosing the presence or absence of PVD.

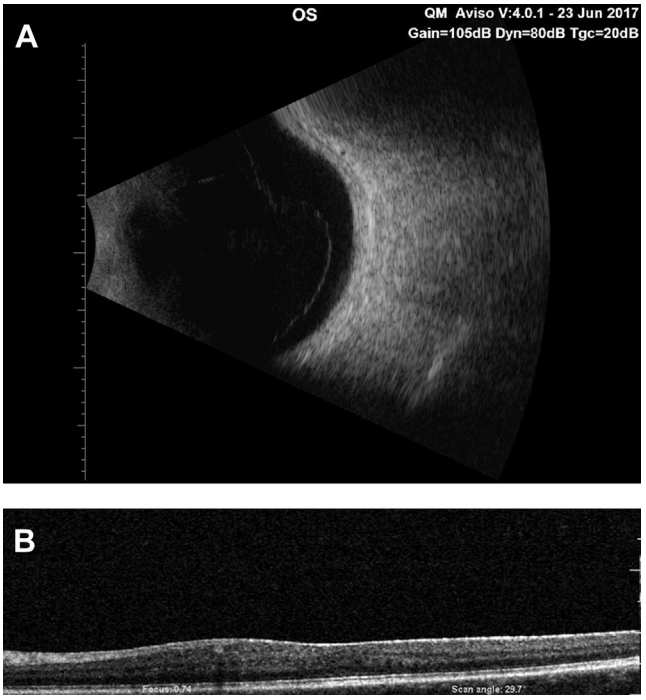

Figure 1. A, Ultrasound image from a 62-year-old man with posterior vitreous detachment (PVD). The typical sigmoid-shaped appearance of a PVD is evident and the detached posterior vitreous cortex is clearly visible anterior to the retina. **B**, Spectral-domain OCT of the same eye as panel **A** shows no evidence of PVD, despite maximizing visualization of the posterior vitreous body by placing the retinal image at the far bottom of the scan.

It is well-known that a PVD often displaces the posterior vitreous cortex so far anteriorly that it cannot be imaged with conventional OCT (Fig 1). In older individuals with AMD, the vitreous is highly liquefied and more prone to farther anterior displacement of the posterior vitreous than in younger individuals.[5] In the absence of perifoveal PVD, spectral-domain OCT alone is unable to distinguish between total attachment of vitreous to the posterior pole and PVD with remote anterior displacement. Thus, in this study many cases of PVD could have been interpreted as total vitreous attachment, introducing inaccuracy and influencing the findings and conclusions, which are inconsistent with previous studies that used ultrasound imaging, as well as OCT to accurately diagnose the state of the vitreoretinal interface. Future studies with swept-source OCT may well be able to distinguish between vitreous attachment and total PVD, as long as imaging is sufficiently anterior to detect a displaced posterior vitreous cortex.

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REPLY: We would like to thank Drs Sebag and Binder for their interest in our work and for the valuable observations regarding the challenge in assessing the vitreomacular interface status.

In our study,[1] the vitreomacular interface was first evaluated at baseline by spectral-domain (SD) OCT and verified longitudinally using the same diagnostic tool through the examinations of further OCT scans obtained in subsequent multiple time points over a mean follow-up of 34 months.

It is well-known that posterior vitreous detachment (PVD) can displace the posterior vitreous cortex so far anteriorly that it cannot be visualized with a conventional OCT scan. Therefore, in our study the absence of any visible track of posterior vitreous cortex was interpreted as a sign of PVD. As specified in the Methods section, in these cases eyes were classified within the PVD group. We are aware of the possible risk of misinterpretation also in the case of total vitreous attachment to the posterior pole. In fact, it could be possible, although rare in patients with a mean age of 77 years, that the hyaloid might be so completely adherent to the underlying macular surface as to be undetectable on an OCT scan; these cases might be misinterpreted as PVD. However, this risk seems to be considerably reduced by multiple evaluations repeated over subsequent time points during a relatively long follow-up. These longitudinal evaluations enhance the chance that the hyperreflective line on the macular surface, which corresponds with the hyaloid, can be detected on OCT scans (Fig 1).

Previous studies have evaluated the accuracy and reliability of SD OCT for the definition of the vitreomacular interface status, reporting a high agreement between ultrasound imaging and SD OCT for the detection of both complete PVD and incomplete PVD.[2] Moreover, SD OCT was found to visualize additional details of the vitreomacular interface that are not discernible with ultrasound imaging, such as focal vitreomacular traction and fine macular changes related to PVD.

As cited in our article,[1] there are a number of previous studies that have investigated the relationship between vitreous and age-related macular degeneration (AMD); some of them have suggested the role of vitreomacular adhesion (VMA) as a risk factor for exudative AMD. Unfortunately, studies that used both ultrasound imaging and OCT are few[3–5] and only one of them was conducted with the SD OCT.[5] This study, which included a consistent number of patients (n = 378), failed to demonstrate a significant difference in the frequency of VMA in eyes with exudative AMD compared with controls (only a trend toward increased frequency was reported). In addition to the limitation correlated with the use of time domain-OCT, the strength of the other studies that used both ultrasound imaging and OCT is weakened by the inclusion of small number of participants[3,4] and/or patients with various stages of AMD that did not allow the differentiation of VMA as a cause or rather as a consequence of AMD.[3,5] For example, Krebs et al[3] evaluated 50 eyes with exudative AMD, 57 with nonexudative AMD, and 56 controls. In this study, the correspondence between choroidal neovascularization site and VMA was assessed by time domain-OCT. Moreover, the exudative AMD group included eyes with evidence of choroidal neovascularization on fluorescein angiography, with no distinction based on disease stage, previous treatments, time of onset, or lesion type. Similarly, although the study by Robison et al[4] distinguished between active and end-stage disease, it included only 39 patients and used different types of OCT, either time domain-OCT or SD OCT.

As stated in our discussion,[1] we are aware of the possible limitation owing to the use of SD OCT alone for the assessment of the vitreomacular interface status. However, taking into account these considerations, we believe the risk that this affects the conclusions of our research is very low.

Therefore, we believe that there is still a lack of conclusive evidence about the relationship between VMA and AMD. Our study

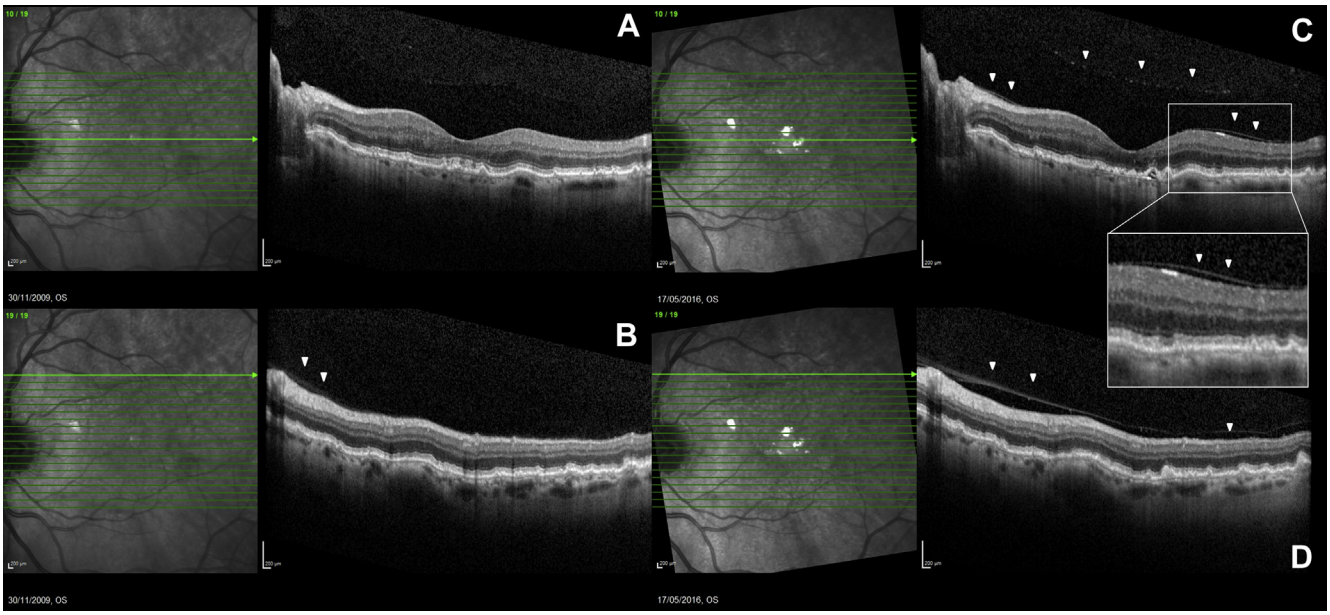

Figure 1. **A**, An OCT scan at baseline does not allow to accurately visualize the hyaloid completely attached to the underlying macular surface; vitreomacular adhesion (VMA) is difficult to detect and the presence of the bursa premacularis is not very evident; this case could have been misinterpreted as a posterior vitreous detachment. **B**, The VMA can be barely hypothesized by the scans through the arcades obtained at the same time point. **C**, **D**, The posterior vitreous cortex is clearly visible on further OCT scans obtained at subsequent time points showing the bursa premacularis and the hyperreflective line on the macular surface, which corresponds to the posterior hyaloid.

suggests that VMA might be a consequence rather than a causative factor in the development of choroidal neovascularization. More longitudinal studies conducted on a greater number of patients with additional diagnostic tools and novel imaging devices will be necessary to draw a definitive conclusion on this topic.

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Re: Singh et al.: Nepafenac 0.3% after cataract surgery in patients with diabetic retinopathy: result of 2 randomized phase 3 studies (*Ophthalmology*. 2017;124:776-785)

TO THE EDITOR: We read the article published by Singh et al[1] with great interest. However, we believe that some discussion is required. The authors present results of 2 studies assessing clinical benefits of nepafenac 0.3% over vehicle in reducing the risk of pseudophakic cystoid macular edema (PCME) in phacoemulsification cataract surgery.

In the methodology section, the authors evaluate the severity of diabetic retinopathy (DR) on fundus photographs obtained at the screening visit as follows: no apparent retinopathy, mild nonproliferative DR (NPDR), moderate NPDR, severe NPDR, and proliferative DR (PDR). However, it is unclear whether patients with no apparent retinopathy and PDR were excluded from the study. And, if PDR patients were excluded, shouldn't the title of the paper clearly manifest that the results refer to NPDR only?

The risk factors of PCME have been recently assessed by Chu et al[2] in a large, retrospective database study of 81 984 surgeries. Eyes of patients with diabetes carried an increased relative risk, which increased proportionately with the severity of DR. Thus, it seems justified to ask whether the authors attempted to find differences between the outcomes in terms of DR severity. This issue has a significant translation into the expected outcome. Modjtahedi et al[3] conducted a multicenter retrospective analysis based on 11 579 patients demonstrating that therapeutic response to topical nonsteroidal anti-inflammatory drugs (ketorolac in 72.4% of the cases) and glucocorticoids (prednisolone in 96.2% of the cases) may vary depending on the severity of DR. Although the treatment was shown to be effective in prevention of PCME in nondiabetic subjects (relative risk, 0.68; 95% CI, 0.58−0.72) and in diabetic patients without retinal complications (relative risk, 0.51, 95% CI, 0.32−0.82), it did not produce expected therapeutic benefits in the DR group (relative risk, 1.06; 95% CI, 0.81−1.38). Moreover, Friedman et al[4] analyzed the efficacy of nepafenac 0.1% in management of non−center-involved diabetic macular edema (DME). One year of topical therapy (3 times a day) did not result in a significant reduction of the edema. These findings imply that cyclooxygenase products may play only a marginal role in the pathomechanism of DME.

Figure 4 in the original article presents a bar graph showing the percentage of patients with best-corrected visual acuity improvement through day 14 and maintained through day 90. Major differences between the results of studies 1 and 2 are presented, with no statistical difference between nepafenac and vehicle in study 2. Did these studies differ in the methodology? Figure 7 presents a graph showing the mean change in best-corrected visual acuity from preoperative baseline to each visit in patients treated with nepafenac 0.3% and vehicle in each study, and in the pooled analysis (full analysis set). However, were there any statistically significant differences between the groups in consequent follow-up visits, particularly in study 2?

The empirical data were analyzed thoroughly and with piety. Readers will certainly—as we did—appreciate the authors' endeavor. However, one could feel unsatisfied when juxtaposing results that spring from the 2 international studies. The rift found is remarkable. The authors mention some post hoc subgroup analyses that aim at identifying the factors (or confounders) that potentially may have confused the issue. In that context, we would like to encourage the authors to carry out, once more, a more in-depth analysis of the underlying problem(s). Please consider, for example, a stepwise regression model, multilevel modeling, and a mixed-effects design. Estimates obtained from the aforementioned "fashion" will enrich the results to date and most likely will help find a factual (and backed up by evidence) explanation for the discussed big discrepancies between the 2 presented studies. We look forward to solving the riddle.

Finally, we believe that evaluating PCME only on the basis of foveal thickness might be inaccurate. It was shown that significant differences in edema morphology in DME and PCME exist.[5] In DME, the pattern of edema might be asymmetric, owing to focal leakage,