To the Editor: We read with great interest the report by Yeung et al regarding the increased hazard among β-blocker (BB) users for neovascular age-related macular degeneration (nAMD).1 Certainly, the frequency with which BB are used makes the results of their study concerning. However, given the potential ramifications, we hope for further clarity on numerous issues regarding the study.

First, several questions arise based on the author’s use of their propensity score. “The propensity score is the probability of treatment assignment (in this case initiation of a BB vs. not) conditional on observed baseline characteristics.”2 It is curious then why the authors chose to make the date of hypertension (HTN) diagnosis as the index date and not the date of BB initiation. With this seemingly innocuous switch, they are introducing a concerning potential source of bias since it is unclear how eligibility of patients would change as covariates change with time.

Additionally, propensity scores balance covariates over the entire matched set, which may not continue to hold true once the authors subdivided cohort 1 into 1A and 1B. Last, it is unclear what the authors intended as the alternative to a propensity of initiating BB therapy. Cohort 2 was defined as “usage of ≥1 non-β-blocker anti-hypertensive medications for ≥270 days per year”3; however, is this someone who is receiving HTN care at baseline without initiation of new anti-HTN therapy? Ideally, the propensity score would have been used to select a patient who had a specific propensity to receive a BB, yet, instead received another class of anti-HTN medication that was selected a priori (such as calcium-channel blockers). This step alone may have improved the distribution of baseline covariates and better equalized the cohorts.4 Furthermore, to create the best comparison, because cohort 1 patients were required to take a BB for a specified amount of time before inclusion, the alternative HTN class of medication should have also been mandated to occur over a similar time frame. This would reduce the “healthy user effect,” because it is well-known that patients who are adherent to medications have different underlying disease risk rates than those who are not compliant.5

Next, although the use of initial HTN diagnosis for the index date allows for a convenient point of comparison across cohorts, this choice introduces other concerns beyond covariate balance. First, it may not accurately reflect the severity of HTN at the time of BB initiation owing to the potentially large gap between the start of study observation time and initiation of BB therapy. How this time in each cohort was accounted for is unclear. It is conceivable that a large gap in time between HTN diagnosis and BB initiation could represent a period of poorly controlled HTN with multiple medication trials. Conversely, it could indicate relatively stable HTN course during which an additional diagnosis (e.g., atrial fibrillation) was made for which BB therapy was indicated in conjunction with maintaining HTN control. Given these uncertainties, it is surprising that the authors felt confident enough to unequivocally state, “Thus, hypertension itself is no longer a confounding factor.”6 Although the authors did attempt to match the cohorts by “hypertension-related end-organ diseases and the number of antihypertensive medications used,”7 no data are reported to support their conclusion that the severity of HTN as a source of bias has been negated.

Last, the number and baseline characteristics of cohort 1 patients who were split into 1A and 1B were never specified, nor do the authors state how many patients (total or by each cohort) developed nAMD. Also of note is how the authors dealt with dry AMD in their cohorts. It is possible that one of the underlying indications for BB use had an independent association with dry AMD, which in turn may have led to an imbalance in the prevalence of dry AMD between the 2 cohorts. If large enough, an unequal distribution of dry AMD between comparators could easily have contributed to the higher hazard ratio for the development of nAMD seen in BB users. Ideally, the authors would have restricted this study to only patients with known dry AMD status because it is a necessary intermediary step to developing nAMD.

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References