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Systemic Beta-Blockers and Risk of Progression to Neovascular Age-related Macular Degeneration

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Abstract

Importance—Beta-blockers (BB) are one of the most commonly prescribed agents for hypertension (HTN) and other indications. The high prevalence BB use among the elderly makes the question of increased risk by BB for neovascular age-related macular degeneration (nAMD) of great public health significance.

Objective—To determine whether oral BB are associated with the development of nAMD.

Design—Retrospective cohort study of patients from 2000–2014.

Setting—Data from a large national U.S. insurer's medical claims database.

Participants—Patients with non-exudative AMD who initiated (index date) a beta-blocker (BB), a calcium channel blocker (CCB), an angiotensin converting enzyme/angiotensin receptor blocker (ACE/ARB), or a diuretic. Patients were excluded for <2 years in the plan prior to the index date, any history of nAMD or diagnosis or treatment for an ocular disease that could be confused with nAMD.

Main Outcome Measures—Hazard of developing of nAMD. Primary analysis compared BB to CCB patients with BB vs. the other classes as secondary analyses. Additionally, a sensitivity analysis was performed between BB and CCB cohorts using 1:1 propensity score matching. Cox proportional hazard regression was performed to estimate the hazard ratio (HR) of developing nAMD at 90, 180 and 365 days for BB. Covariates of interest included demographic information, year of index date, number of anti-hypertensive medications, and other comorbid systemic conditions.

Results—18,754 BB patients and 12,784 CCB patients met criteria for inclusion. After controlling for covariates, patients on BB had a lower hazard for nAMD at both 90 and 180 days than patients on CCB (HRs:0.67–0.71;p<0.01 for both) and diuretics (HRs:0.55–0.62;p<0.01). Patients on BB vs ACE/ARB at all time points and BB vs CCB and diuretics at 365 days did not have a significantly lower association with nAMD (HR:0.73–0.85; p>0.06 for all comparisons). A sensitivity analysis using propensity score matching yielded similar results with patients on BB significantly less likely to develop nAMD at 90 and 180 days (HR:0.70–0.76;p<0.049 for both) but not at 365 days (HR:0.88;p=0.30) compared to patients on CCB.

Conclusions—No evidence was found that BB usage increased the hazard for nAMD relative to other anti-hypertensive medications.

Keywords

Hypertension; age-related macular degeneration; beta-blockers; calcium channel blockers; ACE/ARB inhibitors; diuretics

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in developed nations.¹ It is divided into two types – non-exudative and neovascular. Non-exudative AMD is characterized by drusen, retinal pigment epithelium (RPE) and choriocapillaris atrophy, and geographic atrophy. Neovascular AMD (nAMD) is defined by growth of choroidal neovascularization (CNV), which is responsible for approximately three-fourths of severe vision loss in patients with AMD.²

Beta-blockers (BB) are one of the most commonly prescribed first-line agents for hypertension (HTN), arrhythmias, coronary artery disease, and heart failure. They also have been shown to reduce risk of myocardial infarction, stroke, and death.³ Pre-clinical studies have identified mechanisms through which BB may modulate anti-VEGF levels and development of CNV. For example, metipranolol attenuated zinc-induced RPE and photoreceptor degeneration in rat brain and bovine retinal tissue.⁴ Similarly, BB decreased norepinephrine-induced upregulation of VEGF in brown adipocysts and cardiac monocytes.⁵ With these pathophysiologic mechanisms in mind, it was natural that clinical evaluations testing their relation to VEGF would follow.

To date, clinical studies on the association of BB use and incidence/progression of nAMD have been mixed. Two studies have reported an increased risk of nAMD with BB use, but both only compared BB use to non-use, which does not account for the underlying disease conditions that the BB was intended to treat or other independently associated systemic comorbidities.^{6, 7} Contradicting these findings, no association was found in two cross sectional studies, but due to the nature of cross-sectional studies, it is impossible to know if the development of nAMD predated use of BB.^{8, 9} Studies on anti-VEGF use for the treatment of nAMD are similarly inconsistent with one report suggesting fewer injections were required for patients on BB and another study finding no association.^{10, 11}

The high prevalence of use of BB among the elderly makes the question of increased risk by BB for nAMD of great public health significance. To better address this issue, we conducted a study of the risk of nAMD after initiation of systemic BB using a large national U.S. insurance database.

Methods

Data Set

The Clinformatics Data Mart Database (OptumInsight, Eden Prairie, MN) is a large national U.S. insurer's administrative medical claims database that contains de-identified beneficiary medical claims. It includes all outpatient medical claims, associated diagnoses, pharmaceutical prescriptions filled, and demographic data of beneficiaries during their enrollment in the insurance plan. Since this study involves de-identified data, it was declared exempt from review by the University of Pennsylvania's Institutional Review Board.

Subjects

All patients 55 or older from years 2002–2014 with a diagnosis of non-exudative AMD who had at least two years in the plan were eligible. Patients were then separated into cohorts defined by the initiation of a new HTN medication. Grouping occurred based on the class of the anti-HTN medication: BB, calcium channel blocker (CCB), angiotensin converting enzyme/angiotensin II receptor blocker (ACE/ARB), or diuretic with the index date defined as the date of initiation of the new medication. Our primary analysis compared patients started on BB versus those started on CCB. Secondary analyses compared BB to ACE/ARB and to diuretic medication classes. Furthermore, two sensitivity analyses were performed. The first used a 1:1 match propensity score model between BB and CCB to better equate baseline distribution of demographic variables and indications for use of both medication classes. The score was created to reflect the propensity for being given a CCB (due to fewer patients in that cohort). The second excluded all patients who were censored or developed nAMD within 15 days of the index date (i.e., initiating an anti-HTN medication) to reduce a potential detection bias for sub-clinical nAMD on the index date.

Additional exclusion criteria for all cohorts were a history of any of the following events prior to the index date: nAMD diagnosis or other ocular disease that could be confused with nAMD, any use of anti-VEGF, any intravitreal injection, less than two years of continuous data in the insurance plan, and/or any prescription for a medication from a comparison cohort including topical BB for non-BB cohorts (see eTable 1 for all ICD9 codes used within this study).

Outcomes and Covariates of Interest

The primary outcome was defined as a new diagnosis of nAMD after initiation of the HTN medication class being studied. Covariates of interest were age (modeled individually categorically, as a continuous variable, and as an exponential function of itself), sex, race, year of index date, number of HTN medications, and general comorbid conditions including diabetes, transient ischemic attack (TIA), chronic liver disease, and malignancy and others (eTable 1).

Statistical Analysis

Demographic data and co-morbid conditions were collected at the time of the index date. Mean and standard deviation were used to summarize continuous variables, while frequencies and percentages were used for categorical variables. Cox proportional hazard regression was performed to evaluate the hazard of developing nAMD at 90, 180 and 365 days. Within each individual analysis (e.g. BB vs. CCB, BB vs diuretics), patients were censored for use of a medication from the comparison cohort, gap in prescription coverage of >30 days, eligibility end date, or new diagnosis of a competing ocular disease. Candidate variables for final multivariate modeling were chosen for association ($p < 0.2$) in univariate modeling at 90-days and those *a priori* thought to be clinically significant (e.g., race and sex). Statistical analysis was performed using SAS (version 9.4; SAS Institute Inc., Cary, NC).

Results

31,538 patients were included in the primary study between BB and CCB (Figure 1). 18,754 BB patients had 77, 129, 215 instances of new nAMD at 90, 180, and 365 days, respectively. 12,784 CCB patients had 80, 127, and 179 instances over the same time frames. Table 1 shows the baseline demographics and covariate information for both the BB and CCB cohorts.

Demographic characteristics, comorbid conditions, and indications for treatment with anti-HTN medication were considered in univariate analysis (Table 2). Age, index year of diagnosis, previous ischemic stroke/TIA, peripheral vascular disease, and any malignancy were all chosen for the multivariate modeling after finding associations with the development of nAMD (all had $p < 0.20$).

In the multivariate model, patients using BB were significantly less likely than patients using CCB to develop nAMD at 90 days (HR=0.67, 95% CI=0.49–0.91, $p=0.01$) and 180 days (HR=0.71, 95% CI=0.56–0.92, $p=0.008$), but not at 365 days (HR=0.85, 95% CI=0.70–1.04, $p=0.12$) (Table 3). Age was significantly associated with development of nAMD at all observation periods (every 1 year increase HR=1.04, 95% CI=1.02–1.07, $p < 0.001$ at all time points). In addition, previous ischemic stroke/TIA was associated with significantly decreased hazard of nAMD at 90 days (HR=0.57; 95% CI=0.34–0.95, $p=0.03$), but not at 180 days (HR=0.93; 95% CI=0.67–1.30; $p=0.68$) or 365 days (HR=1.07; 95% CI=0.83–1.39; $p=0.60$).

In secondary analyses, we compared the incidence of nAMD in patients on BB with those using ACE/ARB and diuretics. 5,768 ACE/ARB patients had 34, 58, and 87 instances of new nAMD at 90, 180, and 365 days, respectively, while 3,625 diuretic patients had 28, 42, and 55 instances over the same time frame (Table 3). No association was seen with nAMD in patients using BB vs ACE/ARB over any of the observation periods (HR=0.73–0.83, 95% CI=0.49–1.10, $p=0.06$ –0.22). Compared to patients using diuretics, those on BB were significantly less likely to develop nAMD at 90 days (HR=0.56, 95% CI=0.36–0.86, $p=0.009$) and 180 days (HR=0.64, 95% CI=0.45–0.90, $p=0.01$), but not at 365 days (HR=0.82, 95% CI=0.61–1.10, $p=0.19$).

In order to further limit the impact of differences in baseline covariates between the BB and CCB cohorts, a sensitivity analysis using propensity score matching was performed. This resulted in 11,952 patients being compared in each group (baseline covariates seen in Table 3). With propensity matching adjustment, multivariable analysis results were similar with BB vs CCB users significantly less likely to develop nAMD at 90 days (HR=0.70, 95% CI=0.50–1.00, $p=0.049$) and 180 days (HR=0.76, 95% CI=0.57–1.00, $p=0.046$), but not at 365 days (HR=0.88, 95% CI=0.71–1.11, $p=0.30$).

Numerous other sensitivity analyses were also run. First, we excluded all patients who were censored or developed nAMD within 15 days of starting a BB or CCB. Similar to the primary multivariate analysis, patients on BB ($n=17,462$) vs CCB ($n=11,934$) were significantly less likely to develop nAMD at 90 days (HR=0.68, 95% CI=0.48–0.96, $p=0.03$) and 180 (HR=0.73, 95% CI=0.56–0.95, $p=0.02$) days, but not at 365 days (HR=0.88, 95% CI=0.71–1.09, $p=0.23$). Next, neither including patient age as a categorical variable to accommodate a nonlinear association with risk of CNV nor excluding patients ($n=1001$, 3.7% of total study population) under the age of 55, changed the hazard ratio by more than 0.01 in our primary analysis; there was no evidence of interaction between treatment and age or gender ($p>0.48$), for any of the three outcome periods.

Discussion

With an aging population and a sharp increase with age in incidence of nAMD, efforts aimed at amelioration of nAMD risk are of particular public health importance. To this end, a recent focus has been on the identification of systemic medications that may impact the development of nAMD. One of the most studied classes of systemic medications is anti-hypertensives, and more specifically, BB.^{6–12} Although the association between BB use and development of nAMD has been examined previously, the findings and conclusions have been inconsistent.

Our results do not support the assertion that oral BB use is associated with increased incidence of nAMD. For all comparison groups, development of nAMD in patients using BB was either similar to or significantly lower than in patients on CCB, ACE/ARB, or diuretics (Table 3).

Our primary analysis compared BB to CCB because these classes of medications have the largest overlap in their indications for use. Using CCB as a comparator decreases the possibility that one of the indications for BB use is independently responsible for the association previously reported between their use and development of nAMD rather than the BB themselves. Furthermore, we performed a sensitivity analysis on this comparison using propensity matched scoring, which is an effective way of balancing baseline covariates in cohort studies. Even after controlling for these variables, we found that BB vs CCB users were less likely to have a new diagnosis of nAMD. Decreased incidence of nAMD was also identified in a secondary analysis comparing BB users to patients on diuretics. Although it would seem reasonable to state that BB should be used whenever possible, considerable differences still exist in the indications for each class of anti-HTN medications that would make such a blanket statement difficult to implement. Additionally, while the differences in

these groups were significant, a conservative estimate of our findings suggests that it would take 470 CCB users or 280 diuretic users to instead be started on an oral BB to prevent a single case of nAMD.

In the above-mentioned comparisons, decreased incidence of nAMD in BB vs CCB and diuretic users was found after 90 days and 180 days, but not after 365 days. This represents narrowing of the hazard ratio (moving closer to 1.0) and resolution of any significant effect in all comparison groups with duration in the study. This early “signal” for nAMD may be due to acceleration to nAMD in a group of patients destined to develop nAMD in the first place. As the significant differences in hazard for nAMD are dissipated by 365 days, our results argue against a true “protective effect” for nAMD in the BB groups.

Our data also showed that age was significantly associated with development of nAMD, while a history of previous ischemic stroke/TIA was associated with significantly decreased incidence of nAMD. The identified relationship between ischemic stroke/TIA and nAMD is likely an indicator of overall poorer patient health and decreased likelihood of establishing a diagnosis of nAMD rather than a “protective” effect on development of nAMD.

Untangling which physiologic effects can be attributed to a drug and not to the underlying disease (indication bias) is always a difficult task in studies such as this. Despite not being able to control for specific levels of blood pressure, we used an abundance of caution to deal with hypertensive patients. First, the vast majority of patients in our primary analysis (82%) and even more in the propensity score analysis (92.5%) had HTN. Furthermore, we controlled for the number of HTN medications each patient was on which was also well balanced between the comparison groups. We found no association between these variables and nAMD. This may be due to the overwhelming percentage of patients with HTN making it difficult to determine the overall effect of HTN (since mostly everyone had it). The lack of association in our number of HTN medications variable is consistent with large clinical trial data from AREDS, which showed no difference in risk for nAMD in patients with controlled and uncontrolled HTN.¹³

Our results are in direct contrast to two studies that found a significantly increased risk between BB use and development of nAMD. Klein *et al* used data from the Beaver Dam Eye Study, a population-based study to show a statistically significant higher incident rate ratio of nAMD in oral BB users.⁶ Unlike our study, BB use was compared with BB non-use, which again may have allowed for indication bias to affect the results. Yeung *et al* conducted a retrospective, longitudinal cohort study focused on BB users vs other anti-HTN medication users in the National Health Insurance Research Database in Taiwan, and showed a significantly increased risk for patients on BB.⁷ Several aspects of their methodology raise important questions regarding interpretation of the results.¹⁴ First, no specification was made as to which medications comprised the non-BB comparison group.^{6, 15} Second, no attempt was made to control for non-exudative AMD, which is a mandatory precursor for patients progressing to nAMD. Lastly, the index date was initiation of HTN diagnosis instead of the date of initiation of the anti-HTN medication. This allowed for changes to have occurred between initial treatment for HTN (possibly with another medication than a BB) and start of BB use.

Two other studies that examined this issue were consistent with our hypothesis that beta-blockers do not increase the risk of nAMD. Neither Davis *et al* nor Thomas *et al* found significant differences in anti-HTN medication use in patients with non-exudative AMD and nAMD.^{8, 9} Contrary to the cross-sectional nature of these studies, the cohort design of our study allowed for establishing a temporal relationship between date of systemic medication initiation and diagnosis of nAMD.

The strengths of our study include a large sample cohort drawn across the United States. Despite limiting our study to only those with non-exudative AMD, we were still able to assemble very large cohorts, with 55 to 215 patients with new diagnosis of nAMD after a 365-day observational period depending on the antihypertensive used. Additionally, we stringently controlled for indications for medication initiation and comorbidities (confounding variables). In addition, pharmacy records were used for assessment of medication adherence eliminating self-reporting/recall bias.

Our results should be interpreted in light of several important limitations. Despite using data from a national insurance claims database, the data may not generalize to uninsured patients or those in other insurance networks. We are also limited by the timeframe within the database, and it is unclear if our results would be the same if the study was conducted over a longer observation period. Also, the diagnoses used were based on ICD9 codes and were not verified via medical record review. This limits our ability to verify that the correct diagnosis was made as well as control for important aspects as dry AMD severity. Next, we were unable to precisely control for the indication of each single prescription, meaning that our model may not have fully accounted for potential indication bias. In addition, although the presumption is made that when a patient fills a prescription regularly that the patient is taking the medication, we are unable to verify the actual medication consumption. Also, we were unable to control for duration of non-exudative AMD or features of AMD that are known to have a higher association with development of nAMD (e.g., large soft drusen). Likewise, the database lacks information on smoking status, which has been shown to increase incidence of AMD.¹⁶ While these last two limitations certainly exist, it is unlikely that the decision to offer one of the studied classes of medications was influenced by these factors, which would have had to occur to influence our results. Similarly, although propensity score matching is very good at balancing known covariates, unmeasured confounding may still exist; randomization of a large enough study population generally balances unknown covariates as well. Lastly, we only evaluated patients out to one year; it is unclear how longer duration studies may impact the results.

In conclusion, our study did not show an increased hazard risk for development of nAMD in patients on oral BB therapy. Because of the high prevalence of use of systemic medications in the growing elderly population, additional studies are warranted to investigate the impact of use of other systemic medications on the progression of non-exudative AMD to nAMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Conflicts of Interest: No conflicting relationship exists for any author.

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Brian VanderBeek had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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Key Points**Question**

Is oral beta-blockers (BB) use associated with the development of neovascular age-related macular degeneration (nAMD)?

Findings

Oral BB use was not associated with increased hazard for developing nAMD as compared to other anti-hypertensive agents.

Meaning

Clinicians should feel reassured when prescribing oral BB to patients with non-exudative AMD. The impact of use of other systemic anti-hypertensive medications on the progression of non-exudative AMD to nAMD should be investigated.

Figure 1. Flow chart showing number of excluded and included patients for the primary analysis in our study

Abbreviations: AMD, age-related macular degeneration; VEGF, vascular endothelial growth factor.

Table 1

Baseline covariates for patients taking oral beta-blockers vs calcium channel blockers in primary and sensitivity (propensity score) analysis.

Demographics	Primary Analysis		p-value*	Propensity Score Analysis		p-value*
	Beta blockers (N=18754)	Calcium channel blockers (N=12784)		Beta blockers (N=11952)	Calcium channel blockers (N=11952)	
Age			0.02			0.43
<75	5961 (31.8%)	3918 (30.6%)		3821 (32.0%)	3759 (31.5%)	
75–79	3580 (19.1%)	2570 (20.1%)		2312 (19.3%)	2412 (20.2%)	
80–84	6293 (33.6%)	4229 (33.1%)		3953 (33.1%)	3921 (32.8%)	
>=85	2920 (15.6%)	2067 (16.2%)		1866 (15.6%)	1860 (15.6%)	
Sex			<0.001			0.15
Male	7810 (41.6%)	4702 (36.8%)		4395 (36.8%)	4503 (37.7%)	
Female	10944 (58.4%)	8082 (63.2%)		7557 (63.2%)	7449 (62.3%)	
Race			<0.001			0.95
White	6918 (36.9%)	4756 (37.2%)		4449 (37.2%)	4470 (37.4%)	
Black, Hispanic and Asian	1300 (6.9%)	1138 (8.9%)		937 (7.8%)	940 (7.9%)	
Unknown	10536 (56.2%)	6890 (53.9%)		6566 (54.9%)	6542 (54.7%)	
Index Year			<0.001			0.86
2002–2007	3052 (16.3%)	2019 (15.9%)		2011 (16.8%)	1942 (16.2%)	
2008	1675 (8.9%)	1026 (8.0%)		986 (8.2%)	999 (8.4%)	
2009	2468 (13.2%)	1401 (11.0%)		1395 (11.7%)	1384 (11.6%)	
2010	2353 (12.5%)	1720 (13.5%)		1560 (13.1%)	1586 (13.3%)	
2011	2306 (12.3%)	1680 (13.1%)		1544 (12.9%)	1527 (12.8%)	

Demographics	Primary Analysis			Propensity Score Analysis		
	Beta blockers (N=18754)	Calcium channel blockers (N=12784)	p-value *	Beta blockers (N=11952)	Calcium channel blockers (N=11952)	p-value *
2012	2312 (12.3%)	1680 (13.1%)		1575 (13.2%)	1547 (12.9%)	
2013	2450 (13.1%)	1783 (13.9%)		1571 (13.1%)	1609 (13.5%)	
2014	2138 (11.4%)	1475 (11.5%)		1310 (11.0%)	1358 (11.4%)	
<i>Diabetes mellitus</i>			1.0			0.91
No	13392 (71.4%)	9129 (71.4%)		8565 (71.7%)	8573 (71.7%)	
Yes	5362 (28.6%)	3655 (28.6%)		3387 (28.3%)	3379 (28.3%)	
<i>Previous ischemic stroke or TIA</i>			0.15			0.86
No	15476 (82.5%)	10630 (83.2%)		9957 (83.3%)	9947 (83.2%)	
Yes	3278 (17.5%)	2154 (16.8%)		1995 (16.7%)	2005 (16.8%)	
<i>Previous ICH</i>			0.96			0.36
No	18515 (98.7%)	12622 (98.7%)		11789 (98.6%)	11805 (98.8%)	
Yes	239 (1.3%)	162 (1.3%)		163 (1.4%)	147 (1.2%)	
<i>Chronic liver disease</i>			<0.001			0.82
No	18572 (99.0%)	12742 (99.7%)		11912 (99.7%)	11910 (99.6%)	
Yes	182 (1.0%)	42 (0.3%)		40 (0.3%)	42 (0.4%)	
<i>Chronic pulmonary disease</i>			0.82			0.4
No	11477 (61.2%)	7840 (61.3%)		7405 (62.0%)	7468 (62.5%)	
Yes	7277 (38.8%)	4944 (38.7%)		4547 (38.0%)	4484 (37.5%)	
<i>PVD</i>			<0.001			0.99
No	12794 (68.2%)	9010 (70.5%)		8426 (70.5%)	8427 (70.5%)	
Yes	5960 (31.8%)	3774 (29.5%)		3526 (29.5%)	3525 (29.5%)	

Demographics	Primary Analysis			Propensity Score Analysis		
	Beta blockers (N=18754)	Calcium channel blockers (N=12784)	p-value *	Beta blockers (N=11952)	Calcium channel blockers (N=11952)	p-value *
<i>Any malignancy</i>			0.04			0.65
No	14578 (77.7%)	10059 (78.7%)		9403 (78.7%)	9374 (78.45)	
Yes	4176 (22.3%)	2725 (21.3%)		2549 (21.3%)	2578 (21.6%)	
<i>CKD</i>			<0.001			0.6
No	15569 (83.0%)	10284 (80.4%)		9806 (82.0%)	9837 (82.3%)	
Yes	3185 (17.0%)	2500 (19.6%)		2146 (18.0%)	2115 (17.7%)	
<i>Atrial fib/flutter</i>			<0.001			0.81
No	13675 (72.9%)	10394 (81.3%)		9561 (80.0%)	9576 (80.1%)	
Yes	5079 (27.1%)	2390 (18.7%)		2391 (20.0%)	2376 (19.9%)	
<i>CHF</i>			<0.001			0.68
No	13483 (71.9%)	10695 (83.7%)		9841 (82.3%)	9865 (82.5%)	
Yes	5271 (28.1%)	2089 (16.3%)		2111 (17.7%)	2087 (17.5%)	
<i>Previous MI</i>			<0.001			0.3
No	14783 (78.8%)	11773 (92.1%)		10896 (91.2%)	10941 (91.5%)	
Yes	3971 (21.2%)	1011 (7.9%)		1056 (8.8%)	1011 (8.5%)	
<i>Arrhythmia</i>			<0.001			1.0
No	9990 (53.3%)	8384 (65.6%)		7582 (63.4%)	7582 (63.4%)	
Yes	8764 (46.7%)	4400 (34.4%)		4370 (36.6%)	4370 (36.6%)	
<i>HTN</i>			<0.001			0.19
No	2577 (13.7%)	839 (6.6%)		892 (7.5%)	839 (7.0%)	

	Primary Analysis			Propensity Score Analysis		
	Beta blockers (N=18754)	Calcium channel blockers (N=12784)	p-value *	Beta blockers (N=11952)	Calcium channel blockers (N=11952)	p-value *
Demographics						
Yes	16177 (86.3%)	11945 (93.4%)		11060 (92.5%)	11113 (93.0%)	
<i>Severity of HTN</i>			<0.001			0.28
1	9037 (48.2%)	5454 (42.7%)		5448 (45.6%)	5335 (44.6%)	
2	5814 (31.0%)	4399 (34.4%)		3893 (32.6%)	3924 (32.8%)	
3	3903 (20.8%)	2931 (22.9%)		2611 (21.8%)	2693 (22.5%)	
<i>Number of outcomes</i>			0.01			0.05
90 days	77 (0.4%)	80 (0.6%)		54 (0.5%)	77 (0.6%)	
180 days	129 (0.7%)	127 (1.0%)		90 (0.8%)	121 (1.0%)	
365 days	215 (1.1%)	179 (1.4%)		145 (1.2%)	168 (1.4%)	

* Log rank test

Abbreviations: TIA, transient ischemic attack; ICH, intracranial hemorrhage; PVD, peripheral vascular disease; CKD, chronic kidney disease; CHF, congestive heart failure; MI, myocardial infarction; HTN, hypertension

Table 2

Cox proportional hazard univariate analysis results at the 90-day observation period for developing neovascular age-related macular degeneration.

Covariates	Hazard Ratio	95% CI	p-value
<i>Age</i>	1.03	1.01–1.05	<0.001
<i>Female</i>	1.01	0.73–1.39	0.95
<i>Race (White comparison)</i>			0.41
Black, Hispanic and Asian	0.79	0.42–1.50	
Unknown	0.81	0.58–1.12	
<i>Index Year</i>			0.046
2002–2007	--	--	
2008	1.81	1.03–3.19	
2009	1.00	0.55–1.82	
2010	0.90	0.49–1.66	
2011	1.45	0.84–2.49	
2012	0.92	0.50–1.70	
2013	0.73	0.39–1.40	
2014	0.70	0.35–1.44	
<i>Diabetes mellitus</i>	0.95	0.67–1.35	0.77
<i>Previous ischemic stroke or TIA</i>	0.60	0.36–0.99	0.04
<i>Previous ICH</i>	0.53	0.07–3.80	0.53
<i>Chronic liver disease</i>	Incalculable	--	0.98
<i>Chronic pulmonary disease</i>	1.04	0.75–1.43	0.81
<i>Peripheral vascular disease</i>	0.75	0.53–1.08	0.13
<i>Any malignancy</i>	1.29	0.90–1.84	0.16
<i>Chronic kidney disease</i>	1.25	0.85–1.84	0.25
<i>Atrial fibrillation/flutter</i>	1.10	0.77–1.59	0.59
<i>Congestive heart failure</i>	0.87	0.59–1.29	0.49
<i>Previous myocardial infarction</i>	0.88	0.56–1.38	0.57
<i>Arrhythmia</i>	0.87	0.63–1.20	0.40
<i>Hypertension</i>	0.88	0.54–1.43	0.60
<i>Severity of hypertension (1 medication comparison)</i>	--	--	0.54
2	1.22	0.86–1.75	
3	1.09	0.72–1.64	
<i>Beta-blockers (compared to calcium channel blockers)</i>	0.67	0.49–0.91	0.01

* Bolded are factors selected for multivariate analysis due to $p < 0.2$ or known to have clinical significance for development of nAMD.

Abbreviations: CI, confidence interval; TIA, transient ischemic attack; ICH, intracranial hemorrhage

Table 3

Summary of Cox proportional hazard multivariate analysis** comparing beta-blockers to the other medication classes in relation to development of exudative age-related macular degeneration.

Medication Class	90 day observation period			180 day observation period			365 day observation period		
	N (%) nAMD	Hazard Ratio (95% CI)	p-value	N (%) nAMD	Hazard Ratio (95% CI)	p-value	N (%) nAMD	Hazard Ratio (95% CI)	p-value
Beta-blockers (n=18,754) vs Calcium channel blockers (n=12,784)	77 (0.4%) vs 80 (0.6%)	0.67 (0.49, 0.91)	0.01	129 (0.7%) vs 127 (1.0%)	0.71 (0.56, 0.92)	0.008	215 (1.1%) vs 179 (1.4%)	0.85 (0.70, 1.04)	0.12
Beta-blockers (n=18,754) vs Angiotensin converting enzyme/Angiotensin receptor blockers (n=5,768)	77 (0.4%) vs 34 (0.6%)	0.73 (0.49, 1.10)	0.13	129 (0.7%) vs 58 (1.0%)	0.74 (0.54, 1.01)	0.06	215 (1.1%) vs 87 (1.5%)	0.83 (0.65, 1.08)	0.16
Beta-blockers (n=18,754) vs Diuretics (n=3,625)	77 (0.4%) vs 28 (0.8%)	0.56 (0.36, 0.86)	0.009	129 (0.7%) vs 42 (1.2%)	0.64 (0.45, 0.90)	0.01	215 (1.1%) vs 55 (1.5%)	0.88 (0.71, 1.11)	0.19
Post-propensity Matched Analysis									
Beta-blockers (n=11,952) vs Calcium channel blockers (n=11,952)	54 (0.5%) vs 77 (0.6%)	0.70 (0.50, 1.00)	0.049	90 (0.8%) vs 121 (1.0%)	0.76 (0.57, 1.00)	0.046	145 (1.2%) vs 168 (1.4%)	0.88 (0.71, 1.11)	0.30

* Cox proportional hazard model controlled for age, gender, race, index year, history of stroke or transient ischemic attack, peripheral vascular disease, and any history of malignancy