American Academy of Ophthalmology
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Association between Antiplatelet or Anticoagulant Drugs and Retinal or Subretinal Hemorrhage in the Comparison of Age-Related Macular Degeneration Treatments Trials

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Purpose: To evaluate the association between use of antiplatelet or anticoagulant drugs and retinal or subretinal hemorrhage in participants with neovascular age-related macular degeneration (AMD) in the Comparison of AMD Treatments Trials (CATT).

Design: Cohort study within CATT.

Participants: Participants in CATT with untreated active neovascular AMD (n = 1185).

Methods: Participants were interviewed for use of antiplatelet or anticoagulant drugs. Trained readers evaluated photographs for the presence and size of retinal or subretinal hemorrhage at baseline and years 1 and 2. Associations between use of antiplatelet or anticoagulant drugs and hemorrhage were evaluated among all participants and by baseline hypertension status using multivariate logistic regression models.

Main Outcome Measures: Odds ratio for association with antiplatelet or anticoagulant use.

Results: Among 1165 participants with gradable photographs, 724 (62.1%) had retinal or subretinal hemorrhage at baseline; 84.4% of hemorrhages were 1 disc area (DA) or less, 8.1% were 1 to 2 DA, and 7.5% were more than 2 DA. At baseline, 608 participants (52.2%) used antiplatelet or anticoagulant drugs, including 514 participants (44.1%) using antiplatelets only, 77 (6.6%) using anticoagulants only, and 17 (1.5%) using both. Hemorrhage was present in 64.5% of antiplatelet or anticoagulant users and in 59.6% of nonusers ($P = 0.09$; adjusted odds ratio [OR], 1.18; 95% confidence interval, 0.91−1.51; $P = 0.21$). Neither presence nor size of baseline hemorrhage was associated with the type, dose, or duration of antiplatelet or anticoagulant use. Forty-four of 1078 participants (4.08%) had retinal or subretinal hemorrhage detected on 1- or 2-year photographs; these hemorrhages were not associated with antiplatelet or anticoagulant use at baseline ($P = 0.28$) or during follow-up ($P = 0.64$). Among participants with hypertension (n = 807), antiplatelet or anticoagulant use was associated with a higher rate of hemorrhage at baseline (66.8% vs. 56.4%; adjusted OR, 1.48; $P = 0.01$), but not size of retinal or subretinal hemorrhage ($P = 0.41$).

Conclusions: Most retinal or subretinal hemorrhages in eyes enrolled in CATT were less than 1 DA. Among all CATT participants, antiplatelet or anticoagulant use was not associated significantly with hemorrhage, but it was associated significantly with hemorrhage in participants with hypertension. *Ophthalmology 2015;■:1−9 © 2015 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

The number of people 65 years of age and older in the United States is increasing and is expected to reach 79.7 million by 2040.[1] This population shift carries with it an increased burden of age-related diseases such as cardiovascular disease (CVD) and age-related macular degeneration (AMD).[2] Both antiplatelet drugs such as aspirin and anticoagulant drugs such as warfarin and clopidogrel are used commonly to treat and manage CVD.[3] Use of these antiplatelet or anticoagulant drugs is associated with increased risk of bleeding, including intracerebral and gastrointestinal hemorrhaging.[3−5] However, the effect of antiplatelet or anticoagulant drugs on ocular hemorrhage is less clear. A few studies have investigated the association of antiplatelet or anticoagulant use with ocular hemorrhage among AMD patients,[6−14] but the results from these studies have been conflicting and inconclusive. Because antiplatelet

http://dx.doi.org/10.1016/j.ophtha.2015.09.046
ISSN 0161-6420/15

or anticoagulant drugs are used frequently in older people and ocular hemorrhage generally is associated with poor vision outcome in neovascular AMD,[15–17] a better understanding of the association of antiplatelet or anticoagulant use with ocular hemorrhage is important.

This study evaluated the association between antiplatelet or anticoagulant use and retinal or subretinal hemorrhage among participants in the Comparisons of AMD Treatments Trials (CATT). In the CATT study, a large number of retinal or subretinal hemorrhage cases (n = 608) were identified at baseline from the standard grading of color fundus photographs, and detailed information on the use of antiplatelet or anticoagulant drugs was collected, providing an opportunity to study this association.

Methods

Details on the study design and methods have been reported in our previous publications[18,19] and on ClinicalTrials.gov (identifier NCT00593450). Only the major features related to this article are described here.

Study Participants

The institutional review board associated with each center approved the study protocol (available at: https://www.med.upenn.edu/cpob/studies/documents/CATTManualofProceduresJan2011.pdf), and written consent was obtained from each participant. Participants from 43 clinical centers in the United States were randomized to 1 of the 4 treatment groups: (1) ranibizumab monthly, (2) bevacizumab monthly, (3) ranibizumab as needed (pro re nata [PRN]), and (4) bevacizumab PRN. At 1 year, participants initially assigned to monthly treatment retained their drug assignment but were reassigned randomly to either monthly or PRN treatment. Participants initially assigned to PRN treatment retained both their drug and regimen for year 2.

The study enrollment criteria included patients who were 50 years of age or older with untreated active choroidal neovascularization (CNV) resulting from AMD in the study eye (1 eye per participant) and visual acuity between 20/25 and 20/320 on electronic visual acuity testing. The presence of active CNV, as seen on fluorescein angiography, and fluid, as seen on time-domain optical coherence tomography, located either within or below the retina or below the retinal pigment epithelium was required to establish the presence of active CNV. The study eye was not allowed to have current vitreous hemorrhage or diabetic retinopathy that may require medical or surgical intervention during the 2-year CATT follow-up.

At enrollment, participants provided information on demographic characteristics and a medical history, including a history of CVD and hypertension. At baseline and follow-up visits every 4 weeks, the participants were interviewed by the study coordinator about the use of antiplatelet or anticoagulant drugs, including the name of the drug, administration dose and frequency, and the dates of use. At baseline and 1 and 2 years of follow-up, stereoscopic color photographs and fluorescein angiograms of the macula were obtained from each participant using standard protocols. These images were submitted to the CATT Fundus Photograph Reading Center for grading.

Evaluation of Retinal or Subretinal Hemorrhage

The details on the image grading for color fundus photographs and fluorescein angiography images have been reported.[20] As part of the grading of the CNV lesion characteristics, 2 certified graders in the CATT Fundus Photograph Reading Center, masked to the participants' antiplatelet or anticoagulant use status, independently graded the baseline and follow-up photographic images for the presence and size of retinal or subretinal hemorrhage ($\leq$1, >1–$\leq$2, >2 disc areas [DAs]) in the study eye (Fig 1), regardless of hemorrhage location (retinal, subretinal, or sub–retinal pigment epithelium). Discrepancies between 2 graders were adjudicated by graders. In cases where persisting discrepancies existed, the images were adjudicated by the Fundus Photograph Reading Center principal investigator (J.E.G.). We previously reported the reproducibility of grading of a random sample of 84 image sets,[20] the grading for presence and size of retinal or subretinal hemorrhage (none or $\leq$1, >1–$\leq$2, or >2 DA) had good grade–regrade agreement (percentage agreement, 80%; weighted κ, 0.72; 95% confidence interval [CI], 0.59–0.86) and intergrader agreement (percentage agreement, 85%; weighted κ, 0.74; 95% CI, 0.63–0.83).

Statistical Analysis and Power Consideration

Baseline hypertension was defined as systolic blood pressure at least 160 mmHg or diastolic blood pressure at least 95 mmHg or reported history of or ongoing hypertension. The characteristics between participants with versus without retinal or subretinal hemorrhage at baseline were compared using the independent group *t* test for means and the Fisher exact test for proportions. The association between use of antiplatelet or anticoagulant drugs and retinal or subretinal hemorrhage was assessed among all CATT participants and among subgroups based on hypertension status using the Fisher exact test, the odds ratio (OR), and its 95% CI from univariate and multivariate logistic regression models. In the multivariate logistic regression models, we adjusted for the same baseline covariates as a similar study[6]—age, gender, smoking status, diabetes, medical history of CVD, and CNV in the fellow eye—so that the results could be compared between the 2 studies. The association between use of antiplatelet or anticoagulant drugs and the size of retinal or subretinal hemorrhage at baseline was evaluated using the chi-square test and Cochran-Armitage trend test. The association of antiplatelet or anticoagulant use with presence and size of retinal or subretinal hemorrhage was evaluated for any antiplatelet or anticoagulant use, for each specific type of antiplatelet or anticoagulant drugs, and for the dose and duration of antiplatelet or anticoagulant use. All data analyses were performed using SAS software version 9.4 (SAS Inc, Cary, NC).

For this secondary data analysis, power calculation suggests that the CATT study provided at least 80% power to detect an OR of 1.4 or higher risk of retinal or subretinal hemorrhage at baseline associated with antiplatelet or anticoagulant use and at least 78% power to detect an OR of 2.0 or higher risk of retinal or subretinal hemorrhage during years 1 or 2.

Results

Characteristics of Antiplatelet or Anticoagulant Use

Among 1185 CATT participants, 1165 participants with gradable fundus photographs for determination of retinal or subretinal hemorrhage were included in this study. Among these 1165 participants, 608 (52.2%) used 1 or more antiplatelet or anticoagulant drugs at baseline, including 514 (44.1%) with antiplatelet drugs only, 77 (6.6%) with anticoagulant drugs only, and 17 (1.5%) with both antiplatelet and anticoagulant drugs. Among 608 participants who used antiplatelet or anticoagulant drugs, most (87.2%) took