EPIDEMIOLOGY OF THE ASSOCIATION BETWEEN ANTICOAGULANTS AND INTRAOCULAR HEMORRHAGE IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

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Purpose: To determine the cumulative incidence and annual incidence of intraocular hemorrhage (subretinal hemorrhage or vitreous hemorrhage) in patients with neovascular age-related macular degeneration (AMD) and association with daily antiplatelet or anticoagulant (AP/AC) medication usage (aspirin, clopidogrel, and warfarin), age, gender, hypertension, diabetes mellitus, or bilateral neovascular AMD.

Methods: Retrospective cross-sectional study in a tertiary university setting. Data on 195 eyes of 195 patients without previous intraocular hemorrhage examined over 73 months were reviewed.

Results: Ninety-six of 195 patients (49.2%) were taking daily AP/ACs. Of patients taking daily AP/AC agents, 63.5% had hemorrhage compared with 29.2% of patients not taking (odds ratio = 4.21; 95% confidence interval = 1.42–8.46; \( P < 0.001 \)). The overall annual incidence of intraocular hemorrhage was 0.14% per year. Among patients taking daily AP/AC, the cumulative incidence (61 of 96, 63.5%) and annual incidence (0.10%) of concurrent intraocular hemorrhage were significantly greater compared with patients not taking them (29 of 99, 29.2% and 0.04%, respectively; \( P < 0.0001 \)). Fourteen of 18 patients (77%) taking more than 1 daily AP/AC had occurrence of intraocular hemorrhage. Antiplatelet or anticoagulant usage was an independent risk factor for the development of intraocular hemorrhage. The use of any agent resulted in a significantly increased risk of developing intraocular hemorrhage. Additionally, presence of bilateral neovascular AMD was a significant association in those taking daily AP/ACs, whereas age was a significant association in those not taking daily AP/AC agents.

Conclusion: All three daily AP/AC types were significantly associated with an increased risk of the development intraocular hemorrhage in patients with neovascular AMD, whereas gender, hypertension, and diabetes were not. Age was not significantly associated with hemorrhage in patients taking daily AP/AC agents, whereas the presence of bilateral neovascular AMD was significantly associated with hemorrhage. These findings indicate that the AP/AC use may predispose patients with neovascular AMD to intraocular hemorrhage more so than age and duration of disease alone. While the risk that discontinuing these medicines would pose to the patients’ health may be too great to justify, ensuring that an appropriate medication dosage is maintained should be a priority within this patient population.

RETINA 30:1573–1578, 2010

The percentage of Americans older than 60 years continues to rise, from 16.2% in 2000 to 16.6% in 2006. Life expectancy has also risen steadily to an average of 80.4 years for women and 75.2 years for men. However, with increasing age, the prevalence of chronic diseases, such as coronary artery disease, atherosclerosis, and hypertension, is also increasing, as is the use of medications designed to decrease mortality, such as antiplatelet (AP) and anticoagulant (AC) agents. Ophthalmologists have also become
increasingly aware of potential problems associated with the use of these medications, including hemorrhagic complications, occurring in association with a variety of multispecialty surgical procedures, including vitrectomy surgery and intravitreal injections.

There is also evidence that patients with age-related macular degeneration (AMD) who are taking AP or AC medications may be at an increased risk for hemorrhagic complications including severe submacular or vitreous hemorrhage associated with choroidal neovascularization (CNV). When hemorrhage develops with the subretinal space anterior to Bruch membrane, it leads to photoreceptor destruction secondary to iron toxicity, blockage of nutrient diffusion and clot retraction. Consequent disciform scar formation often leads to permanent visual loss. Surgical management of this situation has resulted in variable outcomes but is generally associated with a poor visual prognosis and a high rate of surgery-associated complications. Given that the number of Americans with AMD is expected to grow to more than 12 million by the year 2020, and the prevalence of AP and AC usage is also likely to rise with an increasing elderly population, the question of whether these agents are independently associated with an increased incidence of intraocular hemorrhage in patients with neovascular AMD becomes increasingly important. There have been a limited number of studies examining the role of AP/ACs in patients with neovascular AMD, and there have been no studies to determine if clopidogrel bisulfate (Plavix; Bristol-Myers Squibb, New York, NY) is associated with an increased intraocular bleeding risk in patients with neovascular AMD. Furthermore, although it seems intuitive that there should be an increased incidence of hemorrhagic complications in this patient population, there are no epidemiologic studies reporting these data in the ophthalmic literature.

Therefore, we sought to determine the cumulative and yearly incidence of intraocular hemorrhage in patients with neovascular AMD and if daily aspirin, clopidogrel, or warfarin sodium (Coumadin, Bristol-Myers Squibb, New York, NY) is an associated risk factor. In addition, we looked for any correlation with other possible risk factors including age; gender; and the presence of hypertension, diabetes mellitus, or bilateral neovascular AMD.

Materials and Methods

University of Chicago Institutional Review Board approval was obtained before carrying out this study (protocol no. 16161A). A retrospective analysis of charts of 256 patients identified with the International Statistical Classification of Diseases-9 (ICD-9) code 362.52, “exudative senile macular degeneration of retina,” was performed for every patient seen between January 2002 and January 2008 (73 months). Inclusion criteria included a history of neovascular AMD and all current medications documented on clinical examination and verified through primary care medical record. Exclusion criteria included any previous intraretinal hemorrhage; lack of documented neovascular disease; and history of trauma, posterior segment surgery, or neovascularization in the study eye not related to neovascular AMD. In patients without previous intraocular hemorrhage, the first occurrence of clinically evident subretinal hemorrhage within one disk diameter of the fovea or vitreous hemorrhage anywhere in one eye was reviewed and recorded (one eye per patient only) as was photographic and angiographic evidence of neovascular AMD and subretinal hemorrhage, in addition to clinical information including total follow-up period; age; gender; presence of diabetes, hypertension, or bilateral neovascular disease; and use of AP/AC at all examinations before and at the time of hemorrhage. For patients taking AP/AC at the time of hemorrhage, follow-up duration was calculated based on the first recorded active clinical medication list that included an AP/AC. Medical records were also reviewed to determine the international normalized ratio values for those taking warfarin. Statistic analysis including multivariate logistic regression (Stata Version 8.2; Stata Corporation, College Station, TX) was performed to determine significance (P < 0.05), odds ratio for developing hemorrhage, and 95% confidence intervals based on the risk factors of total follow-up period; age; gender; presence of diabetes, hypertension, or bilateral neovascular disease, and use of AP/AC. Baseline factors, including age; gender; and the presence of diabetes, hypertension, or
bilateral neovascular disease, were compared between groups using Student’s t-test (Stata Version 8.2).

Results

From the 256 charts identified, 195 patients met entry criteria and were included in this study. Sixty-one charts were excluded for the following reasons or diagnoses: no documented neovascular disease (n = 25), previous posterior segment surgery (n = 13), myopic degeneration (n = 5), previous panretinal photoagulation treatment for proliferative diabetic retinopathy (n = 5), presumed ocular histoplasmosis syndrome (n = 3), polyposidal vasculopathy (n = 3), previous trauma (n = 2), central retinal vein occlusion (n = 1), Sorsby fundus dystrophy (n = 1), angiod streaks (n = 1), ocular toxoplasmosis (n = 1), and serpiginous choroiditis (n = 1).

Of 195 patients, 96 (49.2%) were taking daily AP/ACs during a median follow-up of 27.0 months (range, 1–73 months). The average international normalized ratio was 2.2 (range, 1.2–2.9). Baseline factors that were similar between patients taking or not taking AP/AC agents included median follow-up (28.0 or 21.5 months, respectively; \( P = 0.10 \)), age, gender, presence of hypertension, and presence of bilateral neovascular disease. However, there were significantly more diabetic patients taking AP/ACs compared with those not taking them (Table 1).

Ninety-one patients (46.6%) had an occurrence of intraocular hemorrhage over the 6.08-year study period, meaning that among patients with neovascular AMD, the annual incidence was 0.14%. Among patients taking daily AP/AC, the cumulative incidence (61 of 96, 63.5%) and annual incidence (0.10%) of concurrent intraocular hemorrhage were significantly greater compared with patients not taking them (29 of 99, 29.2% and 0.04%, respectively; \( P < 0.0001 \)). In addition, hemorrhage incidence density was 0.022 and 0.013 per patient-month, for those taking and not taking AP/AC, respectively. Of 18 patients taking more than 1 daily AP/AC, 14 (77%) had occurrence of intraocular hemorrhage. Multivariate logistic regression analysis demonstrated that AP/AC usage, age, and presence of bilateral neovascular AMD were independent risk factors for hemorrhage and had significant odds ratios (Table 2). Seven patients had an occurrence of massive vitreoretinal hemorrhage, and 6 of these patients were on 1 or more AP/AC therapies, implying that the annual incidence of combined subretinal and vitreous hemorrhage was 0.009% in patients using daily AP/ACs and 0.001% in patients not taking them.

Discussion

The overall cumulative incidence, annual incidence, and incidence density of intraocular hemorrhage in patients with neovascular AMD are significantly higher in those taking daily oral AP/AC medications. Although the population in this study is already at risk for ocular hemorrhage by having neovascular AMD, the overall cumulative incidence (63.5%) and annual

### Table 1. Baseline Patient Demographics

| Demographic          | n   | %     | \( P \) (Student’s t-Test) |
|----------------------|-----|-------|---------------------------|
| Gender (male/female) | 79/116 | 41/59 | 0.54                      |
| On AP/AC            | 41/55 | 43/57 |                           |
| Not on AP/AC        | 38/61 | 38/62 |                           |
| Age (years)         | 83.1 | 100   | 0.08                      |
| On AP/AC            | 84.8 | 49.3  |                           |
| Not on AP/AC        | 82.1 | 50.7  |                           |
| AP/AC               | 96   | 49.2  |                           |
| Aspirin             | 80   | 41.0  |                           |
| Clopidogrel         | 18   | 9.2   |                           |
| Warfarin            | 16   | 8.2   |                           |
| Multiple            | 18   | 9.2   |                           |
| Hypertension        | 97/195 | 49.7  | 0.69                      |
| On AP/AC            | 45/96 | 46.8  |                           |
| Not on AP/AC        | 52/99 | 52.5  |                           |
| Diabetes mellitus   | 29/195 | 14.8  | 0.02                      |
| On AP/AC            | 20/96 | 20.8  |                           |
| Not on AP/AC        | 9/99  | 0.9   |                           |
| Bilateral wet AMD   | 106/195 | 54.6  | 0.42                      |
| On AP/AC            | 55/96 | 57.2  |                           |
| Not on AP/AC        | 51/99 | 51.5  |                           |

### Table 2. Multivariate Analysis of Risk Factors

| Independent Variable | Odds Ratio (95% Confidence Interval) |
|----------------------|--------------------------------------|
| Gender               | 1.68 (0.88–3.21)                     |
| On AP/AC             | 1.46 (0.58–3.70)                     |
| Not on AP/AC         | 1.82 (0.72–4.57)                     |
| Age                  | 1.05 (1.00–1.09)                     |
| On AP/AC             | 1.03 (0.97–1.10)                     |
| Not on AP/AC         | 1.05 (1.00–1.11)                     |
| AP/AC                | 4.21 (2.15–8.26)                     |
| Aspirin              | 3.75 (1.88–7.48)                     |
| Clopidogrel          | 8.76 (2.32–32.9)                     |
| Warfarin             | 10.7 (2.45–46.6)                     |
| Multiple             | 12.9 (3.00–55.4)                     |
| Hypertension         | 1.08 (0.53–2.22)                     |
| On AP/AC             | 0.76 (0.22–2.56)                     |
| Not on AP/AC         | 1.41 (0.56–3.58)                     |
| Diabetes mellitus    | 0.62 (0.24–1.60)                     |
| On AP/AC             | 0.82 (0.26–2.59)                     |
| Not on AP/AC         | 0.35 (0.03–3.35)                     |
| Bilateral wet AMD    | 1.96 (1.04–3.70)                     |
| On AP/AC             | 3.47 (1.42–8.46)                     |
| Not on AP/AC         | 1.08 (0.42–2.74)                     |
incidence (0.10%) of hemorrhage are much less compared with previous reports of major or minor systemic hemorrhagic complications (1.2%–7% and 2%–24%, respectively) in patients receiving long-term AC therapy.5,26 These incidences are also less than those noted in another study that reported that 3% of patients, without ocular disease, who were taking warfarin had incidental retinal hemorrhage on dilated eye examination.27 The percentage of patients taking AP/ACs is greater in the present study than in a meta-analysis of 68 patients with hemorrhagic complications associated with AMD reported in the literature from 1965 to 1985 in which 19% to 27% of patients were taking various nonsteroidal antiinflammatory AP drugs, including aspirin, or AC drugs.16 Another report found that 23% of patients with intraocular hemorrhage were taking either AP or AC agents and that AMD patients with massive combined vitreous and subretinal hemor-
hages were 11.6 times more likely to be taking warfarin compared with AMD patients presenting with small subretinal hemorrhage,14 which is comparable to the odds ratio for developing hemorrhage reported in the present study of 10.7 for overall hemorrhage risk. Although no patients were taking clopidogrel, the same previous study14 described a non–statistically significant odds ratio of 2.1 for aspirin in patients with massive intraocular bleeding, whereas our results indicate significant associations of both aspirin and clopidogrel with intraocular hemorrhage. This underscores the importance for ophthalmologists to inquire about specific AP/AC agents and to communicate with the medical specialist about the patient’s AMD status.

This is the first study to report the cumulative incidence and annual incidence of vitreous hemorrhage in patients with neovascular AMD. Six of the seven patients presenting with these massive hemorrhages were on AP or AC therapy. Although uncommon, the visual consequences of such hemorrhages can be devastating and surgical intervention has limited visual outcomes.19–22 Future analysis of other predisposing conditions in addition to AP/AC usage may help identify and develop prophylactic treatment for this uncommon yet devastating complication of AMD.

In patients not using daily AP/ACs, increased age was the only associated risk factor for intraocular hemorrhage. Age is a strongly associated risk factor for the development of CNV in patients with AMD28 and subsequent fibrotic scarring may form a cleavage plane for the development of submacular hemorrhage.14–16,29

The increased risk of hemorrhage associated with patients taking AP/ACs who also had bilateral neovascular AMD in this study may indicate that predisposing systemic reasons for using these agents, such as cardiovascular disease, peripheral arterial disease, deep venous thrombosis, increased serum cholesterol, or other factors that were not analyzed, may play a role in the pathogenesis of AMD and hemorrhage. The fact that significantly more patients who were taking AP/ACs had diabetes also indicates that this condition may have contributed toward the medical indication for these agents.

An Age-Related Eye Disease Study report reported a higher incidence of central geographic atrophy associated with use of antiinflammatory medications including aspirin.30 Our data show that patients taking daily aspirin, the most common AP agent in this and other major studies,5,31 were 3.75 times more likely to develop a subretinal hemorrhage than patients not taking it. Although the role of aspirin in decreasing mortality associated with myocardial infarctions and cerebral vascular accidents is well established,31,32 its role as an antiinflammatory agent and platelet inhibitor in the pathogenesis of AMD remains unclear.

The effect of confounding sources of bias was minimized by using multivariate regression analysis. Misclassification bias was minimized by careful review of medical records and fundus photographs for each subject. Selection bias may have influenced our results because the study was performed at a tertiary university-based referral center, where incidence of intraocular hemorrhage is relatively high, especially because these patients may have been referred for management of their condition.

Another weakness of this study is its retrospective nature; a randomized, prospective, cohort study would have greater power to estimate the relative risk of individual AP or AC medications because the cumulative incidence of intraocular hemorrhage is relatively high. However, the reduced risk of myocardial infarction among patients taking aspirin compared with controls in a previous study would ethically preclude randomization of this agent because of excess cardiovascular risk among the placebo group.33 It would be equally difficult to justify halting the clopidogrel or warfarin that patients may be taking for life-threatening conditions because that may significantly increase patient mortality.

Although intraocular hemorrhage complicating AMD is not as directly life threatening as major complications of AC use, which necessitate hospitalization and blood transfusion, it can have devastating consequences on the remaining visual potential, quality of life, and expenditures of an elderly patient. This has important implications for such therapy initiation and maintenance among AMD patients. Patients with a history of AMD who are at a greater
risk of intraocular hemorrhage, such as those starting warfarin or an additional agent to one they are already taking, should undergo an ophthalmic evaluation with dilated fundus examination at the initiation of treatment. Patients who are identified by their ophthalmologist as being at a higher risk for ocular hemorrhagic complications, especially those with neovascular disease in both eyes, may need to have more frequent follow-up with dilated fundus examinations. Concurrent use of AP/ACs may also have an impact on the decision to increase the frequency of intravitreal injection treatments because regression of subclinical CNV should decrease the likelihood of subretinal or vitreous hemorrhage from occurring. While the risk that discontinuing these medicines would pose to the patients’ health may be too great to justify, the potential interactions with other drugs and ensuring that an appropriate medication dosage and a therapeutic international normalized ratio (for those on warfarin) are maintained should be discussed with the patient and other physicians and health care staff responsible for patient care.

Key words: age-related macular degeneration, anticoagulant, antiplatelet, aspirin, clopidogrel, Coumadin, epidemiology, intraocular hemorrhage, subretinal hemorrhage, vitreous hemorrhage.

Acknowledgments

The authors thank Matthew Georgopulos and Chitra Radhakrishnan for their editorial suggestions on this manuscript.

References

1. 2006 United States Census data. Available at: http://www.census.gov/population/www/popdata.html. Accessed September 12, 2009.
2. 2000 United States census data. Available at: http://www.census.gov/Press-Release/www/2001/demoprofile.html. Accessed September 12, 2009.
3. 2005 United States Centers for Disease Control, life expectancy. Available at: http://205.207.175.93/HDI/Table Viewer/tableView.aspx&ReportId=169. Accessed September 12, 2009.
4. Jneid H, Bhatt DL. Advances in antiplatelet therapy. Expert Opin Emerg Drugs 2003;8:349–363.
5. Lutsep HL. Recent clinical trials of antiplatelet therapy in secondary stroke prevention: expectations and results for application in primary care settings. Am J Med 2009;122:S21–S31.
6. Angiolillo DJ, Bhatt DL, Gurbel PA, Jennings LK. Advances in antiplatelet therapy: agents in clinical development. Am J Cardiol 2009;103:A40–A51.
7. Barequet IS, Sachs D, Priel A, et al. Phacoemulsification of cataract in patients receiving Coumadin therapy: ocular and hematologic risk assessment. Am J Ophthalmol 2007;144:719–723.
8. Benzimra JD, Johnston RL, Jaycock P, et al. The Cataract National Dataset electronic multicentre audit of 55,567 operations: antiplatelet and anticoagulant medications. Eye (London) 2009;23:10–16.
9. Law SK, Song BJ, Yu F, et al. Hemorrhagic complications from glaucoma surgery in patients on anticoagulation therapy or antiplatelet therapy. Am J Ophthalmol 2008;145:736–746.
10. Dayani PN, Grand MG. Maintenance of warfarin anticoagulation for patients undergoing vitreoretinal surgery. Trans Am Ophthalmol Soc 2006;104:149–160.
11. Parkin B, Manners R. Aspirin and warfarin therapy in oculoplastic surgery. Br J Ophthalmol 2000;84:1426–1427.
12. Dayani PN, Siddiqi OK, Holekamp NM. Safety of intravitreal injections in patients receiving warfarin anticoagulation. Am J Ophthalmol 2007;144:451–453.
13. Meyer CH, Eter N. Incidence of ocular hemorrhages in anticoagulated patients receiving repeated intravitreal injections. Am J Ophthalmol 2008;145:386–387.
14. Tilianus MA, Vaandragrer W, Cuypers MH, Verbeek AM, Hoyng CB. Relationship between anticoagulant medication and massive intraocular hemorrhage in age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 2000;238:482–485.
15. Lewis H, Sloan SH, Foos RY. Massive intraocular hemorrhage associated with anticoagulation and age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 1988;226:59–64.
16. El Baba J, Jarett WH II, Harbin TS Jr, et al. Massive hemorrhage complicating age-related macular degeneration. Clinico-pathological correlation and role of anticoagulation. Ophthalmology 1986;93:1581–1592.
17. Weir C, Nolan DJ, Holding D, Hammer H. Intraocular haemorrhage associated with anticoagulant therapy. Acta Ophthalmol Scand 2006;78:492–493.
18. Toth CA, Morse LS, Hjelmeland LM, Landers MB III. Fibrin directs early retinal damage after experimental subretinal hemorrhage. Arch Ophthalmol 1991;109:723–729.
19. Hattenbach LO, Klaas C, Koch FI, Giimpel HOC. Intravenous injection of tissue plasminogen activator and gas in the treatment of submacular hemorrhage under various conditions. Ophthalmology 2001;108:1485–1492.
20. Giansanti F, Eandi CM, Virgili G. Submacular surgery for choroidal neovascularisation secondary to age-related macular degeneration. Cochrane Database Syst Rev. 2009:CD006931.
21. MacLaren RE, Uppal GS, Balagga KS, et al. Autologous transplantation of the retinal pigment epithelium and choroid in the treatment of neovascular age-related macular degeneration. Ophthalmology 2007;114:561–570.
22. Hochman MA, Seery CM, Zarbin MA. Pathophysiology and management of subretinal hemorrhage. Surv Ophthalmol 1997;42:195–213.
23. Friedman DS, O’Colmain BJ, Muñoz B, et al. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004;122:564–572.
24. Watzke RC. Acquired macular disease. In: Duane TD, Jaeger EA, eds. Clinical Ophthalmology. Vol 3. Philadelphia, PA: Harper & Row; 1988:3–4.
25. Schulman S. Clinical practice. Care of patients receiving long-term anticoagulant therapy. N Engl J Med 2003;349:675–683.
26. Levine MN, Raskob G, Landefeld S, Kearon C. Hemorrhagic complications of anticoagulant treatment. Chest 2001;119:S108–S121.
27. Superstein R, Gomolin JE, Hammouda W, et al. Prevalence of ocular hemorrhage in patients receiving warfarin therapy. Can J Ophthalmol 2000;35:385–389.
28. Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group. Risk factors for choroidal neovascularization and geographic atrophy in the complications of age-related macular degeneration prevention trial. Ophthalmology 2008;115:1474–1479.

29. Wolter JR, McWilliams JR. Rupture of diciform macular degeneration causing massive retroretinal hemorrhage. Am J Ophthalmol 1965;59:1044–1047.

30. Clemons TE, Milton RC, Klein R, Seddon JM, Ferris FL III; Age-Related Eye Disease Study Research Group. Risk factors for the incidence of advanced age-related macular degeneration in the Age-Related Eye Disease Study (AREDS). AREDS report no. 19. Ophthalmology 2005;112:533–539.

31. Wolff T, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2009;150:405–410.

32. Hegge KA. Antiplatelet agents for prevention of recurrent ischemic stroke. S D Med 2009;62:15–17.

33. Christen WG, Glynn RJ, Ajani UA, et al. Age-related maculopathy in a randomized trial of low-dose aspirin among US physicians. Arch Ophthalmol 2001;119:1143–1149.