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Epidemiology of the Association between Anticoagulants and Intraocular Hemorrhage in Patients with Neovascular Age-Related Macular Degeneration

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Summary Statement

The cumulative and annual incidence of developing subretinal or vitreous hemorrhage is significantly higher in patients with neovascular AMD who are taking daily aspirin, clopidogrel or warfarin compared to patients not taking these agents. Use of these medications poses a significantly greater odds ratio for developing intraocular hemorrhage than other possible risk factors including age, gender, diabetes, hypertension and bilateral neovascular AMD.

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4 **Abstract**
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6 Purpose: To determine the cumulative and annual incidence of intraocular hemorrhage
7 (subretinal hemorrhage or vitreous hemorrhage) in patients with neovascular age-related
8 macular degeneration (neovascular AMD) and association with daily antiplatelet or
9 anticoagulant (AP/AC) medication usage (aspirin, clopidogrel and warfarin), age, gender,
10 hypertension, diabetes mellitus or bilateral neovascular AMD.
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21 Design: Retrospective, cross-sectional study in a tertiary University setting.
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26 Methods: Data on one hundred and ninety-five eyes of 195 patients without prior
27 intraocular hemorrhage examined over seventy-three months was reviewed.
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33 Results: Ninety-six of 195 (49.2%) patients were taking daily AP/ACs. 63.5% of patients
34 taking daily AP/AC agents had hemorrhage compared to 29.2% of patients not taking
35 (OR= 4.21, 95% CI=1.42-8.46, p<0.001). The overall annual incidence of intraocular
36 hemorrhage was 0.14% per year. Among patients taking daily AP/AC, the cumulative
37 incidence (61/96, 63.5%) and annual incidence (0.10%) of concurrent intraocular
38 hemorrhage was significantly greater compared to patients not taking them (29/99, 29.2%
39 and 0.04%, respectively, p<0.0001). Fourteen of 18 (77%) patients taking more than one
40 daily AP/AC had occurrence of intraocular hemorrhage. AP/AC usage was an
41 independent risk factor for the development of intraocular hemorrhage. The use of any
42 agent resulted in a significantly increased risk of developing intraocular hemorrhage.
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66 Additionally, presence of bilateral neovascular AMD was a significant association in

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those taking daily AP/ACs, whereas age was a significant association in those not taking daily AP/AC agents.

Conclusions: 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. These findings indicate that the AP/AC use may predispose neovascular AMD patients 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.

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4 **Introduction**
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6 The percentage of Americans over the age of 60 years continues to rise, from 16.2%
7 in 2000 to 16.6% in 2006.^{1,2} Life expectancy has also risen steadily to an average of 80.4
8 years for women and 75.2 years for men.³ However with increasing age, the prevalence
9 of chronic diseases such as coronary artery disease, atherosclerosis and hypertension is
10 also increasing, as is the use of medications designed to decrease mortality, such as
11 antiplatelet (AP) and anticoagulant (AC) agents.⁴⁻⁶ Ophthalmologists have also become
12 increasingly aware of potential problems associated with the use of these medications,
13 including hemorrhagic complications, occurring in association with a variety of
14 multispecialty surgical procedures,⁷⁻¹¹ including vitrectomy surgery and intravitreal
15 injections.¹²⁻¹³
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31 There is also evidence that patients with age-related macular degeneration (AMD)
32 who are taking AP or AC medications may be at increased risk for hemorrhagic
33 complications including severe submacular or vitreous hemorrhage associated with
34 choroidal neovascularization (CNV). When hemorrhage enters the subretinal space
35 anterior to Bruch's membrane, it causes photoreceptor destruction secondary to iron
36 toxicity, blockage of nutrient diffusion and clot retraction, disciform scar formation, and
37 may lead to permanent visual loss.¹⁴⁻¹⁸ Surgical management of this situation has
38 resulted in variable outcomes, but is generally associated with a poor visual prognosis
39 and a high rate of surgery-associated complications.¹⁹⁻²² Given that the number of
40 Americans with AMD is expected to grow to more than 12 million by the year 2020,²³
41 and the prevalence of AP and AC usage is also likely to rise with an increasing elderly
42 population, the question of whether these agents are independently associated with an
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4 increased incidence of intraocular hemorrhage in neovascular AMD patients becomes
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6 increasingly important. There have been a limited number of studies examining the role
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8 of AP/ACs in patients with neovascular AMD¹⁴⁻¹⁷ and there have been no studies to
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10 determine if clopidogrel bisulfate (Plavix, Bristol-Myers Squibb, New York, NY) is
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12 associated with an increased intraocular bleeding risk in patients with neovascular AMD.
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14 Furthermore, although it seems intuitive that there should be an increased incidence of
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16 hemorrhagic complications in this patient population, there are no epidemiologic studies
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18 reporting these data in the ophthalmic literature.
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24 Therefore, we sought to determine the cumulative and yearly incidence of intraocular
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26 hemorrhage in patients with neovascular AMD and if daily aspirin, clopidogrel or
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28 warfarin sodium (Coumadin, Bristol-Myers Squibb, New York, NY) is an associated risk
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30 factor. In addition, we looked for any correlation with other possible risk factors
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32 including age, gender, and the presence of hypertension, diabetes mellitus or bilateral
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34 neovascular AMD.
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41 **Materials and Methods**

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43 University of Chicago IRB approval was obtained prior to carrying out this study
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45 (protocol No. 16161A). A retrospective analysis of two-hundred and fifty-six patient
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47 charts identified with the International Statistical Classification of Diseases-9 (ICD-9)
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49 code 362.52 “exudative senile macular degeneration of retina” was performed for every
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51 patient seen between January 2002 and January 2008 (73 months). Inclusion criteria
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53 included a history of neovascular AMD and all current medications documented on
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55 clinical examination and verified through primary care medical record. Exclusion criteria
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4 included any prior intraretinal hemorrhage, lack of documented neovascular disease,
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6 history of trauma, posterior segment surgery or neovascularization in the study eye not
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8 related to neovascular AMD. In patients without prior intraocular hemorrhage, the first
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10 occurrence of clinically evident subretinal hemorrhage within one disk diameter of the
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12 fovea or vitreous hemorrhage anywhere in one eye was reviewed and recorded (1 eye per
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14 patient only) as was photographic and angiographic evidence of neovascular AMD and
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16 subretinal hemorrhage, in addition to clinical information including total follow-up
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18 period, age, gender, presence of diabetes, hypertension or bilateral neovascular disease
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20 and use of AP/AC at all examinations prior to and at the time of hemorrhage. For patients
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22 taking AP/AC at the time of hemorrhage, follow-up duration was calculated based on the
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24 first recorded active clinical medication list that included an AP/AC. Medical records
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26 were also reviewed to determine the international normalized ratio (INR) values for those
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28 taking warfarin. Statistic analysis including multivariate logistic regression (Stata
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30 version 8.2, Stata Corp. College Station, TX) was performed in order to determine
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32 significance ($p < 0.05$), odds ratio (OR) for developing hemorrhage and 95% confidence
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34 intervals (CI) based on the risk factors of total follow-up period, age, gender, presence of
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36 diabetes, hypertension, bilateral neovascular disease or use of AP/AC. Baseline factors,
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38 including age, gender, and the presence of diabetes, hypertension or bilateral neovascular
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40 disease was compared between groups using Student's t-test (Stata version 8.2).
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53 **Results**

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55 From the 256 charts identified, one hundred and ninety-five patients met entry criteria,
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57 and were included in this study. Sixty-one charts were excluded for the following
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4 reasons or diagnoses: no documented neovascular disease (n= 25), prior posterior
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6 segment surgery (n= 13), myopic degeneration (n= 5), prior pan-retinal photocoagulation
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8 treatment for proliferative diabetic retinopathy (n= 5), presumed ocular histoplasmosis
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10 syndrome (n= 3), polypoidal vasculopathy (n= 3), prior trauma (n= 2), central retinal vein
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12 occlusion (n= 1), Sorsby's fundus dystrophy (n= 1), angioid streaks (n= 1), ocular
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14 toxoplasmosis (n= 1) and serpiginous choroiditis (n= 1).
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19 Ninety-six of 195 patients were taking daily AP/ACs (49.2%) during a median follow-
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21 up of 27.0 months (range, 1-73 months). The average INR was 2.2 (range 1.2-2.9).
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24 Baseline factors which were similar between patients taking or not taking AP/AC agents
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26 included median follow-up (28.0 and 21.5 months, p=0.10), age, gender, presence of
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28 hypertension, and presence of bilateral neovascular disease. However, there were
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30 significantly more diabetic patients taking AP/ACs compared to those not taking them
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32 (Table 1).
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36 Ninety-one patients (46.6%) had an occurrence of intraocular hemorrhage over the
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38 6.08 year study period, meaning that among patients with neovascular AMD, the annual
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40 incidence was 0.14%. Among patients taking daily AP/AC, the cumulative incidence
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42 (61/96, 63.5%) and annual incidence (0.10%) of concurrent intraocular hemorrhage was
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44 significantly greater compared to patients not taking them (29/99, 29.2% and 0.04%,
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46 respectively, p<0.0001). In addition, hemorrhage incidence density was 0.022 and 0.013
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48 per patient-month, for those taking or not taking AP/AC respectively. Fourteen of 18
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50 (77%) patients taking more than one daily AP/AC had occurrence of intraocular
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52 hemorrhage. Multivariate logistic regression analysis demonstrated that AP/AC usage,
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54 age and presence of bilateral neovascular AMD were independent risk factors for
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4 hemorrhage and had significant odds ratios (Table 2). Seven patients had an occurrence
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6 of massive vitreoretinal hemorrhage and 6 of these patients were on one or more AP/AC
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8 therapies, implying that the annual incidence of combined subretinal and vitreous
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10 hemorrhage was 0.009% in patients using daily AP/ACs and 0.001% in patients not
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12 taking them.
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19 **Discussion**

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21 The overall cumulative incidence, annual incidence and incidence density of
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23 intraocular hemorrhage in patients with neovascular AMD is significantly higher in those
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25 taking daily oral AP/AC medications. Although the population in this study is one
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27 already at risk for ocular hemorrhage by having neovascular AMD,²⁴ the overall
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29 cumulative (63.5%) and annual incidence (0.10%) of hemorrhage is much less compared
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31 to prior reports of major or minor systemic hemorrhagic complications (1.2-7% and 2-
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33 24%, respectively) in patients receiving long-term anticoagulant therapy.²⁵⁻²⁶ It is also
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35 less than in another study which reported that 3% of patients, without ocular disease, who
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37 were taking warfarin had incidental retinal hemorrhage on dilated eye examination.²⁷ The
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39 percentage of patients taking AP/ACs is greater in the present study than in a meta-
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41 analysis of 68 patients with hemorrhagic complications associated with AMD reported in
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43 the literature from 1965 to 1985 in which 19-27% of patients were taking various non-
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45 steroidal anti-inflammatory AP drugs, including aspirin, or ACs.¹⁶ Another report found
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47 that 23% of patients with intraocular hemorrhage were taking either AP or AC agents and
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49 that AMD patients with massive combined vitreous and subretinal hemorrhages were
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51 11.6 times more likely to be taking warfarin compared to AMD patients presenting with
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4 small subretinal hemorrhage,¹⁴ which is comparable to the OR for developing
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6 hemorrhage reported in the present study of 10.7 for overall hemorrhage risk. Although
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8 no patients were taking clopidogrel, the same previous study described a non-statistically
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10 significant odds ratio of 2.1 for aspirin in patients with massive intraocular bleeding,¹⁴
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12 whereas our results indicate significant associations of both aspirin and clopidogrel with
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14 intraocular hemorrhage. This underscores the importance for ophthalmologists to inquire
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16 about specific AP/AC agents and to communicate with the medical specialist about the
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18 patient's AMD status.
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24 This is the first study to report the cumulative incidence and annual incidence of
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26 vitreous hemorrhage in patients with neovascular AMD. Six of the 7 patients presenting
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28 with these massive hemorrhages were on AP or AC therapy. Although uncommon, the
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30 visual consequences of such hemorrhages can be devastating and surgical intervention
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32 has limited visual outcomes.¹⁹⁻²² Future analysis of other predisposing conditions in
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34 addition to AP/AC usage may help identify and develop prophylactic treatment for this
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36 uncommon, yet devastating complication of AMD.
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41 In patients not using daily AP/ACs, increased age was the only associated risk factor
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43 for intraocular hemorrhage. Age is a strongly associated risk factor for the development
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45 of CNV in patients with AMD²⁸ and subsequent fibrotic scarring may form a cleavage
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47 plane for the development of submacular hemorrhage.^{14-16, 29}
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50 The increased risk of hemorrhage associated with patients taking AP/ACs who also
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52 had bilateral neovascular AMD in this study may indicate that predisposing systemic
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54 reasons for using these agents, such as cardiovascular disease, peripheral arterial disease,
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56 deep venous thrombosis, increased serum cholesterol or other factors which were not
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4 analyzed may play a role in the pathogenesis of AMD and hemorrhage. The fact that
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6 significantly more patients who were taking AP/ACs had diabetes also indicates that this
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8 condition may have contributed toward the medical indication for these agents.
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11 An Age-Related Eye Disease Study report reported a higher incidence of central
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13 geographic atrophy associated with use of anti-inflammatory medications including
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15 aspirin.³⁰ Our data show that patients taking daily aspirin, the most common antiplatelet
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17 agent in this and other major studies^{5,31} were 3.75 times more likely to develop a
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19 subretinal hemorrhage than patients not taking it. Although the role of aspirin in
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21 decreasing mortality associated with myocardial infarctions and cerebral vascular
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23 accidents is well-established,³¹⁻³² its role as an anti-inflammatory agent and platelet
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25 inhibitor in the pathogenesis of AMD remains unclear.
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31 The effect of confounding sources of bias was minimized by using multivariate
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33 regression analysis. Misclassification bias was minimized by careful review of medical
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35 records and fundus photographs for each subject. Selection bias may have influenced our
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37 results since the study was performed at a tertiary university-based referral center, where
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39 incidence of intraocular hemorrhage is relatively high, especially since these patients may
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41 have been referred for management of their condition.
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45 Another weakness of this study is its retrospective nature; a randomized, prospective
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47 cohort study would have greater power to estimate the relative risk of individual AP or
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49 AC medications since the cumulative incidence of intraocular hemorrhage is relatively
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51 high. However, the reduced risk of myocardial infarction among patients taking aspirin
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53 compared to controls in a previous study would ethically preclude randomization of this
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55 agent due to excess cardiovascular risk among the placebo group.³³ It would be equally
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4 difficult to justify halting the clopidogrel or warfarin that patients may be taking for life-
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6 threatening conditions as that may significantly increase patient mortality.
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9 Although intraocular hemorrhage complicating AMD is not as directly life-threatening
10 as major complications of anticoagulant use which necessitate hospitalization and blood
11 transfusion, it can have devastating consequences on the remaining visual potential,
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13 quality of life and expenditures of an elderly patient. This has important implications for
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15 such therapy initiation and maintenance among AMD patients. Patients with a history of
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17 AMD who are at greater risk of intraocular hemorrhage, such as those starting warfarin or
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19 an additional agent to one they are already taking should undergo an ophthalmic
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21 evaluation with dilated fundus exam at the initiation of treatment. Patients who are
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23 identified by their ophthalmologist as being at a higher risk for ocular hemorrhagic
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25 complications, especially those with neovascular disease in both eyes, may need to have
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27 more frequent follow-up with dilated fundus examinations. Concurrent use of AP/ACs
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29 may also have an impact on the decision to increase the frequency of intravitreal injection
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31 treatments, since regression of subclinical CNV should decrease the likelihood of
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33 subretinal or vitreous hemorrhage from occurring. While the risk that discontinuing these
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35 medicines would pose to the patients' health may be too great to justify, the potential
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37 interactions with other drugs and ensuring that an appropriate medication dosage and a
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39 therapeutic INR (for those on warfarin) is maintained should be discussed with the
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41 patient and other physicians and health care staff responsible for patient care.
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TABLES

Table 1: Baseline patient demographics.

Table 2: Multivariate analysis of risk factors.

TABLE 1. Baseline patient demographics.

TABLE 1. Baseline patient demographics.			
Demographic	N	%	t-test p-value
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	

Abbreviations: OR, odds ratio; CI, confidence interval; AP/AC, antiplatelet or anticoagulant; AMD, age-related macular degeneration.

TABLE 2. Multivariate analysis of risk factors.

TABLE 2. Multivariate analysis of risk factors.	
Independent Variable	Odds Ratio (95% CI)
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)

CI, confidence interval; AP/AC, antiplatelet or anticoagulant; AMD, age-related macular degeneration.

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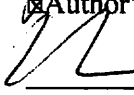
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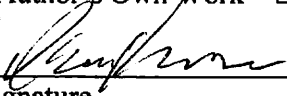
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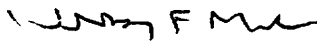
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