

MACULAR DEGENERATION AND ASPIRIN USE

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Purpose: To review current literature of the benefits that aspirin provides for patients' cardiovascular health compared with the risk of AMD worsening.

Methods: We performed a review and critically analyzed six cardiovascular and four ophthalmological trials regarding risks and benefits of aspirin use. The prospective randomized cardiovascular trials had a cumulative 167,580 while the 3 smaller ophthalmological data sets had a cumulative 12,015 subjects.

Results: The reviewed meta-analysis literature demonstrated a statistically significant 32% reduction in the risk of nonfatal stroke with regular aspirin users. The study also documented that aspirin users decreased the risk of fatal vascular deaths by 15%. Of the three ophthalmological studies highlighting the adverse affects of aspirin association with AMD, all suggested an exacerbation of AMD without statistical significance and broad confidence bands.

Conclusion: Overall, the number, size, and quality of the cardiovascular studies recommending aspirin use are far superior to the fewer, smaller and conflicting studies suggesting a possible adverse effect of aspirin use in relation to AMD. The benefits of aspirin usage include preserving the duration and quality of life by decreasing stroke and heart attack risk. These benefits seem to far outweigh the theoretical risks of possibly exacerbating wet AMD, which can be reasonably controlled with anti-VEGF therapy.

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Macular Degeneration and Aspirin Use

Recent press releases regarding the potential adverse effects of aspirin on macular degeneration have caused patients with age-related macular degeneration (AMD) to discontinue their aspirin use without consulting their physician.^{1,2} There are many benefits to aspirin use, and therefore many reasons patients should continue taking the recommended aspirin dose prescribed by their primary physician or cardiologists. As with any treatment, it is important to weigh the risk/benefit ratio of aspirin use, especially in generally elderly and high-risk populations. The benefits of aspirin have long been well documented and highly recommended for the prevention and treatment of

cardiovascular diseases (CVDs), such as myocardial infarction, stroke, and death. The recent retrospective epidemiological eye studies suggesting that aspirin use may exacerbate macular degeneration are based on three limited studies, while the benefits of aspirin use for macular degeneration patients have been suggested in larger studies, including Age-Related Eye Disease Study (AREDS), the Physicians Health Study (PHS), Women's Health Study (WHS).¹⁻⁴ Therefore, the data regarding the effects of aspirin on AMD are conflicting and inconclusive.

Aspirin and Age-Related Macular Degeneration: General Overview

Aspirin is a classical nonsteroidal anti-inflammatory drug, which works through both cyclooxygenase (COX)-dependent pathways and COX-independent pathways.⁵ Aspirin has various pharmacological effects and it is logical to conclude that aspirin could produce some effects on AMD in which the pathophysiology is still unclear. Among risk factors for AMD are smoking, previous cataract surgery, age,

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and family history.⁶ Direct evidence about relation between aspirin use and the development or exacerbation of AMD is unproven and the possible effects of aspirin on AMD from current experimental research can only be presumed.

Large Cardiovascular Studies

A review of numerous epidemiological and prospective randomized and placebo-controlled studies concerning aspirin use has been conducted to establish the benefits of aspirin in the prevention of CVDs. A meta-analysis study using nine published trials by the Antithrombotic Trialists' Collaboration, including the Physician's Health Study (PHS), Hypertension Optimal Treatment Study (HOT), Primary Prevention Project (PPP), and Asymptomatic Atherosclerosis Trial (AAAT), highlights the effectiveness of aspirin in primary prevention of cardiovascular events. Ninety thousand individuals were analyzed among the 9 trials; 50,868 subjects were treated with aspirin and 49,170 received placebo/control.⁷ Meta-analysis of total cardiovascular events shows significant advantage of aspirin over placebo ($P < 0.005$). Table 1 further illustrates all 9 primary prevention trials with statistical significance of cardiovascular end points.

Another meta-analysis study used 5 published trials, including the British Doctors' Trial and Thrombosis Prevention Trial, containing 55,580 randomized participants showed a 32% reduction in the risk of nonfatal stroke (OR: 0.68; 95% CI, 0.59–0.79) with regular aspirin users.⁴ The study also documented that

aspirin users decreased the risk of vascular events by 15% (OR: 0.85; 95% CI, 0.79–0.93).⁸

In another updated study-wide meta-analysis of 11 primary prevention trials (n = 118,335), aspirin use was associated with reductions in nonfatal myocardial infarction (RR, 0.78; 95% CI, 0.71–0.87).⁹ In the 8 trials (n = 87,524) in which aspirin dose was tested, statistically significant reduction in nonfatal total stroke was recorded (RR, 0.86; 95% CI, 0.76–0.98).⁹

Critical issues with meta-analysis studies are selection and identification of studies and heterogeneity of studies. Though these are true, the CVD versus AMD meta-analyses mentioned above incorporate a variety of studies with positive and negative conclusions to avoid selection bias. Each CVD study included in the meta-analysis is focused on a certain population and the confidence interval bands are small (Table 1 and Figure 1).

AMD Epidemiological Studies

Ten studies, including the anti-aspirin studies Blue Mountain Eye Study (BMES) and European Eye Study (EES), involving 171,729 individuals studying the association of aspirin use with AMD risks were analyzed.^{1,2,10–17} Random-effect meta-analysis of studies concluded that aspirin use provided neither beneficial nor harmful effects on AMD and is not associated with AMD risk (relative risk [RR], 1.09; 95% confidence interval [CI], 0.96–1.24; I^2 , 67.3%).¹⁸ In addition, subgroup analyses were performed by AMD stages, adjustment status, country,

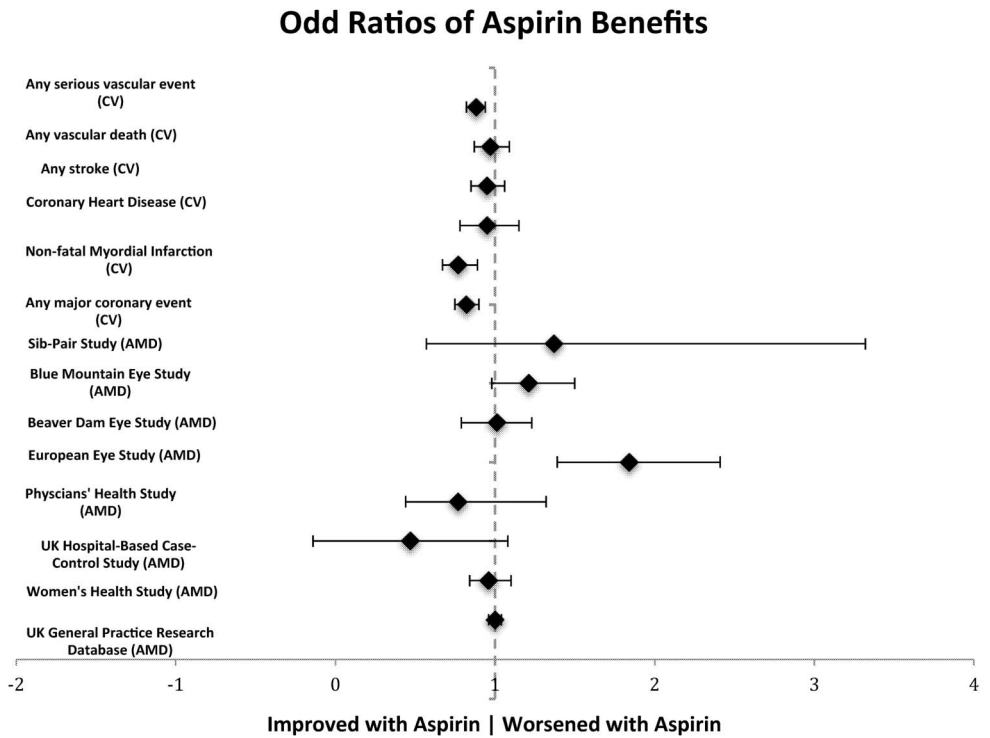
Table 1. CV Studies vs. AMD Studies: Statistics

Study Type	Study	Study Size	Odds Ratio/Relative Risk	Confidence Interval
CV Studies	BMD	5,139	1.023	0.820–1.275
	PHS (CV)	22,071	0.769	0.656–0.900
	TPT	5,085	0.741	0.565–0.972
	HOT	18,790	0.824	0.690–0.985
	PPP	4,495	0.72	0.483–1.075
	WHS	39,876	0.912	0.804–1.034
	AAAT	28,980	0.956	0.735–1.244
	POPADAD	1,276	0.967	0.720–1.298
	JPAD	2,539	0.865	0.562–1.332
AMD Studies against aspirin use	Blue Mountain Eye Study (BMES)	2,389	2.46	1.25–4.83
	European Eye Study (EES)	4,691	wet AMD 1.26; Grade 2, 1.42	1.61–3.05; 1.18–1.70
	Beaver Dam Eye Study (BDES)	4,926	2.2	1.20–4.15

Placebo-controlled randomized cardiovascular studies shown above with large study sizes and restricted confidence intervals. Age-related macular degeneration studies highlighting adverse affects of aspirin are shown in the table above. Small study sizes and broad confidence intervals are shown.

AMD, age-related macular degeneration; CV, cardiovascular.

Fig. 1. The proportional effects of aspirin (an antiplatelet) on numerous cardiovascular events (myocardial infarction [MI], stroke, or vascular death) in the Antithrombotic Trialists' (ATT) Collaboration study are shown above. The diamonds represent the odds ratio of the high-risk events while the horizontal lines demonstrate the 95% confidence intervals for each category. The odds ratio of the Blue Mountains Eye Study (by Liew et al), the Beaver Dam Eye Study (by Klein et al), and the European Eye Study (by de Jong et al) are also illustrated above to provide the association between aspirin and AMD. The Physicians' Health Study (by Christen et al), UK hospital-based case-control study (by Rudnicka et al), and Women's Health Study (by Christen et al) show the positive association between aspirin and AMD. All results to the left of the dashed line represent the benefits of aspirin for patients with risk for vascular events while any data to the right of the dashed line show the negative effect of aspirin for AMD patients. AMD, age-related macular degeneration; CV, cardiovascular.



smoking status, study type, and hypertension and hyperlipidemia status. Results of the analysis of stages of AMD revealed that aspirin use was corrected with neither early stage (RR, 1.02; 95% CI, 0.87–1.29; $P = 0.872$; I^2 , 54.7%) nor late stage AMD (RR, 1.11; 95% CI, 0.77–1.60; $P = 0.587$; I^2 , 0.00%).¹⁸ No associations were detected in a randomized control trial (RCT) group when subgroup analyses were conducted according to study types (RR, 0.81; 95% CI, 0.64–1.02; I^2 , 0.00%), the cohort group (RR, 1.17%; 95% CI, 0.96–1.14; I^2 , 0.00%), and the case-control group (RR, 1.02; 95% CI, 0.92–1.14; I^2 , 44.8%). These results indicate that aspirin use is unlikely associated with risk of AMD.¹⁸

Specific Smaller AMD Epidemiological Studies

The three ophthalmological studies suggesting adverse effects of aspirin on AMD are the BMES, the European Eye Study, and the Beaver Dam Eye Study (BDES).

The BMES database contained 2,389 individuals, but only 257 were regular aspirin users (10.8%). A post hoc analysis was performed to determine if regular aspirin use interacted with age-related macular degeneration. This study was conducted over a 15-year period in which only 63 of the 2,389 developed neovascular AMD. Their results suggested that regular

aspirin users had a 2.5-fold increase in neovascular AMD compared with nonusers, but no significant association was found between aspirin and geographic atrophy (dry AMD).¹⁹ The increase in neovascular AMD (wet AMD) progressed from 1.9% in 5 years, 7% in 10 years, and 9.3% in 15 years in regular aspirin users (OR: 2.46; 95% CI, 1.25–4.83; $n = 257$).¹⁹

The European Eye Study pooled 4,691 participants at 65 years of age and older, collected by random sampling. They found that early AMD was present in 36.4% of the participants and late AMD was present in 3.3% of participants. They also stated that with regular aspirin use, the odds ratios increased with the severity of the AMD ($n = 839$; Grade 1, 1.26 (95% confidence interval [CI], 1.08–1.46; $P < 0.001$); Grade 2, 1.42 (95% CI, 1.18–1.70), and wet late AMD, 2.22 (95% CI, 1.61–3.05).¹² They reported that with early AMD, only Grades 1 and 2, but not Grade 3, were associated with aspirin use. They found no association between aspirin use and pooled early or late AMD, nor with late AMD in those older than 85 years.¹²

The Beaver Dam Eye study is a longitudinal population-based study performed every 5 years for a 20-year period containing 4,926 participants between the ages of 43 and 86 years old.¹⁷ Regular aspirin use, 10 years before retinal examination ($n = 1,462$), was associated with late AMD ($n = 58$; [HR], 1.63 [95% CI, 1.01–2.63]; $P = 0.05$) and with estimated incidence

of 1.76% (95% CI, 1.17–2.64) in regular users and 1.03% (95% CI, 0.70–1.51) in nonusers. Regular aspirin use 10 years before retinal examination was significantly associated with neovascular AMD ($n = 58$; HR, 2.20 [95% CI, 1.20–4.15]; $P = 0.01$) but not pure geographic atrophy ($n = 24$; HR, 0.66 [95% CI, 0.25–1.95]; $P = 0.45$). Aspirin use 5 years (HR, 0.86 [95% CI, 0.71–1.05]; $P = 0.13$) or 10 years (HR, 0.86 [95% CI, 0.65–1.13]; $P = 0.28$) before retinal examination was not associated with incident early AMD.¹² Also, aspirin use 5 years before incidence was not associated with incident early or late AMD.¹²

Limitations in the AMD Epidemiological Studies

The BMES has several limitations as noted by the authors. The dose of aspirin each participant consumed was not collected and thus it was assumed that every “regular user” consumed 150 mg daily based on most Aspirin prescriptions in Australia. Different brands however have different dosages available and Aspirin can be bought without prescription. Additionally, length of exposure to aspirin was not accurately accounted for. Patient recollection of usage is subject to recall error and reported usage for certain year does not guarantee usage preceding years. The size of the regular aspirin users in the cohort study ($n = 257$) was small and not randomized. There was a small number of late AMD cases ($n = 63$) and only 56% of the participants had follow-up examinations at the 15-year mark.²⁰ The reasons for taking aspirin were unaccounted for. Comorbidities are more likely for those taking aspirin and increased use for other conditions was considered but not controlled for adequately. The cohorts were not balanced with respect to age, incidence of stroke, heart diseases, and diabetes; this is important because these groups have a significantly higher incidence of aspirin intake.²⁰

The BMES has been over-interpreted because of excessive media commentary focusing on the 2.5 factor of increased risk of developing wet AMD when patients take aspirin. However, the absolute risk over 15 years is 9.3% with aspirin users and 3.7% for those not taking aspirin.^{18,20,21} No conclusions were drawn about correlation in the BMES, and the authors note that the results do not reach statistical significance when adjusted for other risk factors (BMI, blood pressure, diabetes mellitus, blood total cholesterol level, and fish consumption).¹⁹

Another study indicating AMD risk with aspirin use is The Beaver Dam Eye Study, which contains numerous limitations as noted by the authors.¹⁷ Six hundred and ninety-three regular aspirin users participated in the study of which 58 developed late AMD.

Regular aspirin users were defined as participants who took aspirin at least twice per week for over 3 months, with a cumulative dose of only 24 pills. These criteria may not properly define a regular aspirin user.¹⁷ Similar to the BMES, aspirin users may have taken considerably larger amounts of the drug during the course of the study and aspirin use in these individuals may have been for CVDs or arthritis treatment or those at high risk for these diseases. Confounding factors such as CVD were not included, such as hyperlipidemia history or cholesterol, triglyceride, and lipoprotein cholesterol levels. It is likely that subjects who regularly use aspirin have higher blood lipid levels than those who do not use aspirin and high cholesterol is thought to contribute to AMD pathogenesis.²² Also, it is important to note that geographic atrophy and neovascular AMD are two distinct disorders with different pathophysiology, risk factors, and genetic background. The authors considered the two groups a single entity when evaluating for association of aspirin use.^{23,24} Considering the inherent risk of bias in observational studies and the limitations in group definition and statistical analysis, the association between regular aspirin use and neovascular AMD may be a product of Type I error.¹⁶ This is a claim supported by the inability of authors to confirm such relationships in auxiliary analyses. The authors also suggested that aspirin has no effect on AMD risk at the 5-year mark of the study unlike the 10-year data.¹⁷

The European Eye Study, also a post hoc analysis, contained a small sample size of regular aspirin users ($n = 839$) of which only 45 developed late AMD. Their results had an extremely wide confidence interval due primarily to the small sample size. In this study, the authors also note a possibility that people with AMD took aspirin after experiencing visual problems.¹² There is no data regarding the quantity of the aspirin the subjects used (i.e., 81 mg vs. 300 mg). Additionally, the authors did not eliminate the potential influence of cardiovascular deaths or angina in the analyses.¹² There is also no data on other morbidities, such as arthritis, for which aspirin may have been prescribed. The authors also suggested that aspirin has no effect on AMD risk at the 5-year mark of the study unlike the 10-year data.¹²

Studies Finding No Adverse Effects of Aspirin on AMD

The Physicians' Health Study 1 (PHS1) reported that there was no increase in AMD during 7 to 10 years among regular aspirin users. In this randomized prospective placebo controlled trial, a total of 22,071 participants enrolled in the baseline and a minimum of

7-year follow-up was conducted. Ten thousand six hundred and seventeen were regular aspirin users of which 51 cases of age-related maculopathy (ARM) in the aspirin group and 66 in the placebo group (RR, 0.77; 95% CI, 0.54–1.11). For age-related maculopathy with vision loss, there were 25 cases in the aspirin group and 32 in the placebo group (RR, 0.78; 95% CI, 0.46–1.32).¹ These data demonstrated the protective effects of aspirin and that people taking aspirin were less likely to develop macular degeneration than those taking placebo.¹

The Age-Related Eye Disease Study reported that aspirin is actually beneficial in the protection of dry AMD patients.^{3,4,25} Age-Related Eye Disease Study, a larger study, shows the possible benefits of aspirin use for macular degeneration. Age-Related Eye Disease Studies 1, 3, and 19 have noted that the association between aspirin and AMD is not statistically significant.^{3,4,25} The case-controlled Age-Related Eye Disease Study (AREDS) reported that the use of anti-inflammatory medications, including aspirin, did have a protective effect on dry AMD.²⁵

A recent review and meta-analysis demonstrated that there were no differences that exist between novel oral anticoagulants and other antithrombotic drugs for risk of substantial intraocular bleeding.²⁶ In the Comparison of AMD Treatments Trials (CATT), Martin et al attempted to seek the association between use of anticoagulant/antiplatelet and retinal hemorrhage.²⁶ Among 1,165 participants with active neovascular AMD, they found no significant association between the use of antiplatelet/anticoagulant with retinal hemorrhage at baseline.²⁶

Conclusion

The BMES, the European Eye Study, and the Beaver Dam Eye Study received great deal of attention in the press without the adequate context and consequences being explained to the public and to the medical community. The risk for developing macular degeneration increases with aging. The small and still unconfirmed added risk of AMD is far outweighed by the solid benefits of cardio-protective aspirin. The Beaver Dam Eye Study cannot conclude for certain if aspirin causes late-life vision loss. Cardiovascular diseases or an underlying inflammatory condition may affect individuals in these studies who may be at higher risk for developing AMD because of aspirin use. Additionally, individuals with CVD or history of CVD are more susceptible to develop AMD.⁶ Thus, it is difficult to disentangle whether this is because of aspirin or underlying risk factors that lead people to use aspirin.^{1,2}

Even if aspirin use were confirmed as an AMD risk factor using more robust study data, it is already apparent that the risk would be quite small in absolute terms, at about 1% for aspirin users, and 0.5% for nonusers, which is not clinically meaningful.¹⁷ There are currently good treatment options for neovascular AMD, yet for CVDs and other like conditions, aspirin is one of the main treatment options. Age-related macular degeneration and aspirin association are extremely limited and the presumptions that have been made are not based on persuasive empirical data. Several problems, such as the definition of aspirin use, the inclusion and exclusion of the participants and the required long-term follow-up, makes it hard to conclude the confirmatory relationship between aspirin use and AMD. In the studies mentioning the adverse effects of aspirin on AMD, confounding factors are not accounted for, which are crucial to making any conclusions.

Overall, the number, size, and quality of the studies recommending aspirin use are much greater than the few studies suggesting a possible adverse effect of aspirin use. This is reflected in the much tighter confidence intervals as shown in Figure 1 of benefits of aspirin use. Additionally, many AMD studies that monitor AMD progression per couple years have data preceding optical coherence tomography (OCT) usage, which affects accurate diagnosis and monitoring of AMD. However, the studies suggesting subjects to discontinue aspirin are post hoc analyses with small subject sizes and extremely wide confidence intervals. Substantial evidence exists to support the conclusion that the benefits of aspirin in decreasing the risk of serious medical conditions such as stroke, heart attack, and death outweigh the potential minor increase in incidence of wet AMD possibly associated with aspirin use. Patients who are taking aspirin for cardiovascular health should not fear the possible, theoretical and exaggerated risks of exacerbating their AMD. The inaccurate press releases have endangered the public by frightening many of the nation's elderly into discontinuing their needed prescribed aspirin use, which may be the difference between life and death.

Key words: aspirin, dry AMD, cardiovascular, coronary, vascular, stroke, wet AMD.

References

1. 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.
2. Christen WG, Glynn RJ, Chew EY, et al. Low-dose aspirin and medical record-confirmed age-related macular degeneration in a randomized trial of women. *Ophthalmology* 2009; 116:2386–2392.

3. Chew EY, Clemons T, Sangiovanni JP, et al. The Age-Related Eye Disease Study 2 (AREDS2): study design and baseline characteristics (AREDS2 report number 1). *Ophthalmology* 2012;119:2282–2289.
4. Age-Related Eye Disease Study Research Group. Risk factors associated with age-related macular degeneration: a case-control study in the age-related eye disease study: Age-Related Eye Disease Study Report Number 3. *Ophthalmology* 2000;107:2224–2232.
5. Vane JR, Botting RM. The mechanism of action of aspirin. *Thromb Res* 2003;110:255–258.
6. Chakravarthy U, Wong TY, Fletcher A, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. *BMC Ophthalmol* 2010;10:31–43.
7. Bartolucci AA, Tendera M, Howard G. Meta-analysis of multiple primary prevention trials and cardiovascular events using aspirin. *Am J Cardiol* 2011;107:1796–1801.
8. Eidelman RS, Hebert PR, Weisman SM, et al. An update on aspirin in the primary prevention of cardiovascular disease. *Arch Intern Med* 2003;163:2006–2010.
9. Mora S, Ames JM, Mason JE. Low-dose aspirin in the primary prevention of cardiovascular disease. *JAMA* 2016;316:709–710.
10. Douglas JJ, Cook C, Chakravarthy U, et al. A case-control study of drug risk factors for age-related macular degeneration. *Ophthalmology* 2007;114:1164–1169.
11. Rudnicka AR, MacCallum PK, Whitelocke R, et al. Circulating markers of arterial thrombosis and late-stage age-related macular degeneration: a case-control study. *Eye* 2010;24:1199–1206.
12. De Jong PT, Chakravarthy U, Rahu M, et al. Associations between aspirin use and aging macula disorder: European Eye study. *Ophthalmology* 2012;119:112–118.
13. Hirvelä H, Luukinen H, Läärä E, et al. Risk factors of age-related maculopathy in a population 70 years of age or older. *Ophthalmology* 1996;103:871–877.
14. Wang JJ, Mitchell P, Smith W, et al. Systemic use of anti-inflammatory medications and age-related maculopathy: Blue Mountain Eye study. *Ophthalmic Epidemiol* 2003;10:37–48.
15. DeAngelis MM, Lane AM, Shah CP, et al. Extremely discordant sib-pair study design to determine risk factors for neovascular age-related macular degeneration. *Arch Ophthalmol* 2004;122:575–580.
16. Moon BG, Joe SG, Hwang JU, et al. Prevalence and risk factors of early-stage age-related macular degeneration in patients examined at a health promotion center in Korea. *J Korean Med Sci* 2012;27:537–541.
17. Klein KBK, Howard KP, Gangnon RE, et al. Long-term use of aspirin and age-related macular degeneration. *JAMA* 2012;308:2469–2478.
18. Zhu W, Wu Y, Xu D, et al. Aspirin use and risk of age-related macular degeneration: a meta-analysis. *PLoS One* 2013;8:e58821.
19. Liew G, Mitchell P, Wong TY, et al. The association of aspirin use with age-related macular degeneration. *JAMA Intern Med* 2013;173:258–264.
20. Kaul S, Diamond GA. Relationship of aspirin use with age-related macular degeneration: association or causation? comment on “the association of aspirin use with age-related macular degeneration.” *JAMA Intern Med* 2013;173:264–266.
21. Baignet C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trials. *Lancet* 2009;373:1849–1860.
22. Cougnard-Grégoire A, Delyfer MN, Korobelnik JF, et al. Elevated high-density lipoprotein cholesterol and age-related macular degeneration: the Alienor study. *PLoS One* 2014;9:e90973.
23. 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.
24. Sobrin L, Ripke S, Yu Y, et al. Heritability and genome-wide association study to assess genetic differences between advanced age-related macular degeneration subtypes. *Ophthalmology* 2012;119:1874–1885.
25. Clemons TE, Milton RC, Klein R, et al. 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.
26. Ying GS, Maguire MG, Daniel E, et al. Association between antiplatelet or anticoagulant drugs and retinal hemorrhage in the comparison of AMD treatment trials (CATT). *Ophthalmology* 2016;123:352–360.