Published in final edited form as:

Retina. 2019 October ; 39(10): 1965–1972. doi:10.1097/IAE.0000000000002295.

Association between Oral Iron Supplementation and Retinal or Subretinal Hemorrhage in the Comparison of Age-Related Macular Degeneration Treatments Trials

Delu Song[1], **Gui-Shuang Ying**[1], **Joshua L. Dunaief**[1], **Rupak Bhuyan**[1], **Yafeng Li**[1], **Maureen G. Maguire**[1], **Juan E Grunwald**[1], **Ebenezer Daniel**[1], **Stephanie Hagstrom**[2], **Daniel F Martin**[2], **the Comparison of Age-Related Macular Degeneration Treatment Trial Research Group**[*]

[1]Scheie Eye Institute, Department of Ophthalmology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania University of Pennsylvania, Philadelphia, Pennsylvania

[2]Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio.

Summary statement:

Since patients often take oral iron supplements without medical indication, and no study has investigated the potential side effects of oral iron supplements use to the retina. We performed this post-hoc secondary analysis of CATT data. Our analysis shows for the first time that oral iron supplement use is associated with higher risk of retinal/subretinal hemorrhage in eyes with neovascular AMD, and the association was dose-dependent, particularly among those with hypertension.

Abstract

Purpose: Since patients often take iron supplements without medical indication, and iron can accumulate in vascular endothelial cells, we evaluated the association of oral iron supplementation with retinal/subretinal hemorrhage in patients with neovascular age-related macular degeneration (AMD).

Methods: A post-hoc secondary data analysis of Comparison of AMD Treatments Trials (CATT) was performed. Participants were interviewed for use of oral iron supplements. Trained readers evaluated retinal/subretinal hemorrhage in baseline fundus photographs. Adjusted odds ratios (aORs) from multivariate logistic regression models assessed association between iron use and baseline hemorrhage adjusted by age, gender, smoking, hypertension, anemia and use of antiplatelet/anticoagulant drugs.

[*]A listing of the Comparison of Age-Related Macular Degeneration Treatments Trials Research Group is available at www.aaojournal.org.

Correspondence: Gui-Shuang Ying, PhD, Perelman School of Medicine, University of Pennsylvania, 3535 Market Street, Suite 700, Philadelphia, PA 19104., gsying@pennmedicine.upenn.edu, Phone: 215-615-1514, Fax: 215-615-1531.

Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

All the work for the secondary data analysis that leads to this paper was done in University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Results: Among 1165 participants, baseline retinal/subretinal hemorrhage was present in the study eye in 71% of 181 iron users and in 61% of 984 participants without iron use (aOR=1.47, p=0.04), and the association was dose-dependent (adjusted linear trend p=0.048). Iron use was associated with hemorrhage in participant with hypertension (aOR=1.87, p=0.006) but not without hypertension. The association of iron use with hemorrhage remained significant among hypertensive participants without anemia (aOR=1.85, p=0.02).

Conclusions: Among CATT participants, use of oral iron supplements was associated with retinal/subretinal hemorrhage in a dose-response manner. Unindicated iron supplementation may be detrimental in patients with wet AMD.

Keywords

AMD; oral iron supplements; retinal/subretinal hemorrhage

Introduction

Age-related macular degeneration (AMD) is a common eye condition and a leading cause of vision loss among people aged 50 or older [1]. Early stage (dry AMD) is diagnosed by the presence of medium-sized drusen. One of the late stages, neovascular AMD (wet AMD), is characterized by abnormal blood vessel growth underneath the retina. These vessels can leak fluid and blood, causing swelling and damage to the macula. Neovascular AMD is the most common disease associated with retinal/subretinal hemorrhage. [2]

Oral iron supplements are widely used by patients with anemia, even after the anemia is cured, while iron-containing multivitamins/minerals are commonly used by non-anemic, well-nourished individuals without concern for potential risks. Such extensive use of iron raises questions regarding safety and any unintended side effects. Previous studies have shown that both local and systemic iron overload contribute to AMD-like retinal degeneration in mice [3–5] and humans [6–8]. In mice, intravenous iron elevates retinal vascular endothelial cell iron [3], which could cause dysfunction of vascular endothelial cells leading to retinal hemorrhage.

The present study investigated the association of oral iron supplementation with retinal/subretinal hemorrhage among participants in the Comparisons of AMD Treatments Trials (CATT), a multicenter clinical trial of anti-VEGF treatments for neovascular AMD.

Methods

Details on the study design and methods have been reported in previous publications [9,10] and on ClinicalTrials.gov (identifier NCT00593450). Only the major features related to this study are described here.

Study Participants and Study Procedure

The institutional review board associated with each participating center approved the study protocol and written consent was obtained from each participant.[10]

Participants from 43 clinical centers in the United States were enrolled and randomized to 1 of 4 treatment groups: (1) ranibizumab monthly, (2) bevacizumab monthly, (3) ranibizumab as needed (pro re nata [PRN]), and (4) bevacizumab PRN. The study enrollment criteria included patients who were above 50 years old, diagnosed with AMD and active choroidal neovascularization (CNV) in the study eye and have not been treated previously; and visual acuity in study eye was from 20/25 to 20/320. The presence of active CNV was defined by lesion of CNV shown by fluorescein angiography, fluid seen on optical coherence tomography, located within or below the retina or below the retinal pigment epithelium (RPE). Participants with vitreous hemorrhage or diabetic retinopathy that may need medical or surgical intervention in the study eye were not eligible for the study.

At enrollment, participants provided information on demographic characteristics and medical history, including history of smoking, cardiovascular diseases, hypertension and anemia (classified as: none, past, or ongoing). The participants were interviewed by the study coordinator about the use of iron supplements at baseline including iron multivitamins/minerals, name of iron supplement, administration dose and frequency. The fundus photographs and fluorescein angiograms of the macula were submitted to the CATT reading center for grading.

Evaluation of Retinal or Subretinal Hemorrhage

As described previously[11], color fundus photographs and fluorescein angiographs were graded by two certified graders independently, who were masked to the participants' iron use status, for the presence and size of retinal/subretinal hemorrhage (≤1, >1 to ≤2, or >2 disc areas [DAs]). Discrepancies between two graders were adjudicated by a third grader or the CATT reading center principal investigator (J.E.G). The reproducibility results of grading of a random sample of 84 image sets were published previously [11]. Specifically, 80% grade-regrade agreement (weighted kappa, 0.72) and 85% inter-grader agreement (weighted kappa, 0.74) were achieved in the grading for presence and size of retinal/subretinal hemorrhage.

Statistical Analysis

The two sample t-test and the Fisher exact test were used to compare for means and proportions of characteristics between participants use versus do not use iron supplements at baseline. The associations between any iron supplement use (yes/no), iron dosage per day (no use, <18mg [typical iron dose in multivitamins], 18–36 mg, >36 mg) and retinal/subretinal hemorrhage were assessed among all CATT participants, among those without past history or on-going anemia, and stratified by hypertension status and number of risk alleles for complement factor H (CFH). The odds ratio (OR), and its 95% confidence interval (95% CI) for their association were calculated from univariate and multivariate logistic regression models. In the multivariate logistic regression models, we adjusted for the same baseline covariates as our previous study of antiplatelet/anticoagulant drugs and retinal/subretinal hemorrhage in CATT [12] including age, gender, smoking status, diabetes, dietary supplement use, medical history of cardiovascular disease, and CNV in the fellow eye. In addition, we also adjusted for use of antiplatelet or anticoagulant that was previously found to be associated with retinal/subretinal hemorrhage[9] and the anemia status (no, past,

on-going) that was associated with iron use. The association between use of iron supplements and the size of retinal/subretinal hemorrhage at baseline was evaluated using the chi-square test and Cochran-Armitage trend test. All data analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC), and two-sided $p<0.05$ was considered to be statistically significant.

Results

Characteristics of participants with and without iron use at baseline

Among 1185 CATT participants, 20 participants were excluded due to unreadable fundus photographs. Of the remaining 1165 participants, 984 (84.5%) did not use iron supplements at baseline, 181 (15.5%) used either iron-containing multivitamins/minerals (n=163, 14.0%) or prescriptions (n=18, 1.5%). The most common iron prescription was ferrous sulfate (n=11, 61.1%).

The comparisons of characteristics between participants with versus without iron supplement use at baseline are summarized in Table 1. Participants who used iron supplements were older (mean± SD, 80.2±6.9) than participants who did not use iron (79.0±7.6) (p=0.04), more likely taking AREDS supplement than non-iron users (82.9% vs. 59.6%, P<0.0001), and more likely using antiplatelet or anticoagulant medications (59.1% vs. 50.9%, p=0.04). History of cardiovascular diseases was more prevalent in iron users than non-iron users (32.6% vs. 22.1%, P=0.002). Of the 984 patients without iron use, 834 (90.9%) were not anemic, 42 (4.3%) had anemia in the past, and 48 (4.9%) had ongoing anemia. Among 181 participants with iron use, 127 (70.2%) did not have anemia, 25 (13.8%) had previous anemia, and 29 (16.0%) had ongoing anemia (p<0.0001).

Association between iron supplement use and retinal or subretinal hemorrhage at baseline

While no differences were found in visual acuity, retinal thickness, and size of CNV between CATT participants with and without iron use (data not shown). Interestingly, retinal/subretinal hemorrhage was present in 128 (70.7%) iron users and in 596 (60.6%) non-iron users (p=0.004). This difference remained significant in a multivariate analysis (adjusted OR=1.47, 95% CI, 1.02–2.13, p=0.04, Table 2). The association of iron use with retinal/subretinal hemorrhage was dose-dependent (65% for <18mg, 70% for 18–36 mg, 76% for >36 mg, adjusted linear trend p=0.048, Table 2). In particular, using 18–36 mg of iron was significantly associated with higher risk of retinal/subretinal hemorrhage (adjusted OR=1.66, 95% CI: 1.01 – 2.73, p=0.046) when compared to non-iron users.

Association of iron supplement use with retinal or subretinal hemorrhage by baseline hypertension status

In participants with hypertension at baseline (n=802), 94 of 128 (73.4%) participants with iron use and 406 of 674 (60.2%) without iron use had retinal/subretinal hemorrhage (p=0.005). This association was significant in multivariate analysis (adjusted OR=1.87, 95% CI: 1.19–2.92, p=0.006). Further analysis revealed a dose-dependent risk of hemorrhage (adjusted linear trend p=0.009, Table 2). In particular, hypertensive participants with iron

dose of 18–36 mg had a significantly higher risk of hemorrhage (adjusted OR=1.84, 95% CI: 1.03–3.28, p=0.04, Table 2).

Among subjects without hypertension at baseline, iron use was not associated with retinal/subretinal hemorrhage (adjusted OR=0.87, p=0.68, Table 2). The interaction for association with hemorrhage between iron use and hypertension was not statistically significant in the multivariate model (p=0.11).

Association of iron supplement use with retinal or subretinal hemorrhage in participants without anemia

Since anemia itself can cause retinal hemorrhage, we performed further analysis by excluding all participants with past or ongoing anemia (n=144). Among 1021 participants without anemia at baseline, 84 of 127 (66.1%) iron users and 532 of 894 (59.5%) non-iron users had retinal/subretinal hemorrhage (adjusted OR=1.43; 95% CI: 0.95–2.14, p=0.09, Table 3).

When 1021 participants without anemia were stratified by the baseline hypertension status, iron use was significantly associated with hemorrhage among those with hypertension (adjusted OR=1.85, 95% CI: 1.12 – 3.05, p=0.02), but was not significant among those without hypertension (p=0.81). Dose of 18–36 mg iron was significantly associated with higher risk of hemorrhage among those with hypertension (adjusted OR = 2.05, 95% CI, 1.07–3.92, p=0.03) (Table 3)

Association of iron supplement use with retinal or subretinal hemorrhage in participants with Various AMD SNPs

In order to investigate if the association of iron with hemorrhage was affected by SNP variations, we analyzed the SNPs associated AMD including CFH Y402H (rs1061170), ARMS2 (rs10490924), HTRA1 (rs11200638), C3 (rs2230199), LIPC (rs10468017), CFB (rs4151667), and C2 (rs547154). [13,14] In the 835 CATT participants who were genotyped, we did not find that risk alleles in *ARMS2, HTRA1, C3, LIPC, CFB and C2* exacerbate the retinal/subretinal hemorrhage among the iron using CATT participants. However, CATT participants with risk allele of CFH tend to have higher risk of retinal/subretinal hemorrhage. Among iron users, retinal/subretinal hemorrhage occurred in 21 (67.7%) of 31 participants with no risk allele of CFH, in 38 (66.7%) of 57 participants with one risk allele, and in 31 (77.5%) of 40 participants with two risk alleles (linear trend p=0.34). Among the participants with two risk alleles of CFH (n=265), iron use was significantly associated with higher risk of hemorrhage in univariate analysis (OR=2.25, p=0.04) and was borderline significant in multivariate analysis (adjusted OR=2.17; 95% CI: 0.94–5.01, p=0.07, Table 4), but association was not significant among participants with one (p=0.38) or zero CFH risk alleles (p=0.67). The interaction between iron use and CFH for the association with retinal or subretinal hemorrhage was not statistically significant in the multivariate analysis(p=0.21).

Association of iron supplement use with size of retinal or subretinal hemorrhage

Iron use was associated with larger size of retinal/subretinal hemorrhage (linear trend p=0.01, Table 5). Higher dose of iron use was associated with larger hemorrhage (linear trend p=0.007). The percentage of hemorrhage greater than 1 DA was 9.2% among non-iron users, 10% among iron users with dose less than 18 mg, 13.8% among those with dose of 18–36 mg, and 14.3% among those with dose greater than 36 mg.

Discussion

The potential contribution of iron to the development of AMD has been recognized for over a decade [7,8]. Several case reports have described patients who developed retinal degeneration after intramuscular or intravenous iron therapy [3,15,16]. However, no study has investigated whether oral iron supplements can affect the retina. Our analysis shows for the first time that oral iron supplement use is associated with higher risk of retinal/subretinal hemorrhage in eyes with neovascular AMD, and the association was dose-dependent, particularly among those with hypertension.

Because anemia can cause retinal hemorrhage, we performed additional analysis by excluding all participants with history of or on going anemia and still found a significant association between iron supplements use and retinal/subretinal hemorrhage. This finding is clinically important and indicates that non-anemic neovascular AMD patients who take oral iron supplements may be at risk of retinal/subretinal hemorrhage. This risk is increased in participants with hypertension (OR=1.85, p=0.02), but not so in participants without hypertension (OR=0.86, p=0.81). This significant association of iron use with retinal/subretinal hemorrhage was strongest among those taking iron dose of 18–36 mg (OR=2.05, p=0.03). However, these results should be interpreted with caution, as it is unclear why non-anemic CATT participants (127 out of 1021) also used iron supplements. It is possible some comorbidities in CATT participants, like chronic kidney disease and heart failure, could potentially confound our findings.

Over half of US adults aged 20 years or older take at least one dietary supplement [17,18] despite nutrients from fortified food. Dietary supplement use is most common among older people, women, whites, and highly educated individuals. Over the counter supplements are often self-prescribed or recommended by nurses and dietitian without clear medical indications[19,20]. Of note, the iron-containing multivitamin/multimineral is the most common dietary supplement[18]. Thus it is important to increase awareness of the potential side effects of non-indicated oral iron supplements.

In a previous study, we found iron levels were most increased in the RPE and choroid in mice treated with intravenous iron [3]. Prior to our study, Cibis et al had reported [16], in dogs with repeated intravenous iron injection, that granular iron deposits form in the endothelial cells and choroid stromal histiocytes. More specifically, the terminal branches of the short and long posterior ciliary arteries were a preferential site of the granular iron deposits. Vessel lumens in the choriocapillaris appeared obstructed due to swelling of the iron-laden endothelial cells [16]. In a patient who had received about 150 blood transfusions for the treatment of severe aplastic anemia, complete obstruction of capillaries in the retina and the

choriocapillaris was detected. The main site of granular iron deposits included endothelial cells or macrophages and perivascular tissue in the choroid [16]. Together, these findings suggest a potential mechanism of retinal/subretinal hemorrhage related to oral iron supplements; it is possible that in neovascular AMD patients taking iron supplements, within neovascular vessels, iron toxicity in vascular endothelial cells predisposed to hemorrhage.

Single nucleotide polymorphism in the human CFH gene (Y402H) is significantly associated with increased risk of AMD [21–24]. Our previous analysis showed CATT patients with a higher number of risk alleles for CFH had decreased total thickness of the retina [25]. Interestingly, the present analysis shows among patients with two risk alleles of CFH, taking iron supplements was borderline-significantly associated increased risk of retinal/subretinal hemorrhage (adjusted OR=2.17, p=0.07), but the association was not significant among patients with one risk allele (adjusted OR=1.34, p=0.38) or no risk allele (adjusted OR=1.28, p=0.67). The pathophysiology could involve a combination of complement dysregulation and iron supplementation. A recent study by Ueda et al showed that dysfunction of CFH can lead to thrombotic microangiopathy in multiple organs including the retina [26]. In addition, a study by Li et al showed that iron treatment increases both complement C3 mRNA and protein levels in RPE cells in cell culture and in mice [27]. Thus, in patients with AMD, environment (iron supplements) may interact with genetics (CFH risk) to damage vascular endothelial cells within the retina. Further investigations are warranted to elucidate the mechanisms of iron and complement dysregulation on RPE and retinal vascular endothelial cells.

In summary, in this post-hoc secondary analysis of CATT data, we found that among all CATT participants with neovascular AMD, use of oral iron supplements was significantly associated with retinal/subretinal hemorrhage at baseline in a dose-dependent manner, and particularly among patients with hypertension, iron supplementation was associated with nearly twice the risk of retinal/subretinal hemorrhage. These results argue that in addition to considering well-known side effects of iron use, such as gastrointestinal discomfort, clinicians should be aware of the potential risk of retinal/subretinal hemorrhage among neovascular AMD patients taking oral iron supplements. The results of this secondary analysis of CATT data indicate a need for validating the findings with future investigations of the risk of retinal/subretinal hemorrhage with iron supplementation in AMD populations and in other populations.

Acknowledgement

Supported by the National Center for Advancing Translational Sciences of the NIH (KL2TR001879), NEI/NIH, Bethesda, Maryland (cooperative agreement nos.: U10 EY017823, U10 EY017825, U10 EY017826, U10 EY017828, and R21EY023689), Research to Prevent Blindness, the FM Kirby Foundation, the Paul and Evanina Bell Mackall Foundation Trust.

Abbreviations and Acronyms:

AMD	age-related macular degeneration
CATT	Comparison of Age-Related Macular Degeneration Treatments Trials

CI	confidence interval
CNV	choroidal neovascularization
DA	disc area
OR	odds ratio
PRN	pro re nata

References

1. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. Bull World Health Organ. 2004;82(11):844–851. doi:/S0042-96862004001100009 [PubMed: 15640920]
2. Shultz RW, Bakri SJ. Treatment for submacular hemorrhage associated with neovascular age-related macular degeneration. Semin Ophthalmol. 2011;26(6):361–371. doi: 10.3109/08820538.2011.585368 [PubMed: 22044334]
3. Song D, Kanu LN, Li Y, et al. AMD-like retinopathy associated with intravenous iron. Exp Eye Res. 2016;151:122–133. doi:10.1016/j.exer.2016.08.008 [PubMed: 27565570]
4. Hadziahmetovic M, Dentchev T, Song Y, et al. Ceruloplasmin/hephaestin knockout mice model morphologic and molecular features of AMD. Invest Ophthalmol Vis Sci. 2008;49(6):2728–2736. doi:10.1167/iovs.07-1472 [PubMed: 18326691]
5. Hahn P, Qian Y, Dentchev T, et al. Disruption of ceruloplasmin and hephaestin in mice causes retinal iron overload and retinal degeneration with features of age-related macular degeneration. Proc Natl Acad Sci U S A. 2004;101(38):13850–13855. doi:10.1073/pnas.0405146101 [PubMed: 15365174]
6. Biesemeier A, Yoeruek E, Eibl O, Schraermeyer U. Iron accumulation in Bruch's membrane and melanosomes of donor eyes with age-related macular degeneration. Exp Eye Res. 2015;137:39–49. doi:10.1016/j.exer.2015.05.019 [PubMed: 26026877]
7. Dunaief JL. Iron induced oxidative damage as a potential factor in age-related macular degeneration: the Cogan Lecture. Invest Ophthalmol Vis Sci. 2006;47(11):4660–4664. doi:10.1167/iovs.06-0568 [PubMed: 17065470]
8. Hahn P, Milam AH, Dunaief JL. Maculas affected by age-related macular degeneration contain increased chelatable iron in the retinal pigment epithelium and Bruch's membrane. Arch Ophthalmol Chic Ill 1960. 2003;121(8):1099–1105. doi:10.1001/archopht.121.8.1099
9. CATT Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;364(20):1897–1908. doi: 10.1056/NEJMoa1102673 [PubMed: 21526923]
10. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012;119(7):1388–1398. doi: 10.1016/j.ophtha.2012.03.053 [PubMed: 22555112]
11. Grunwald JE, Daniel E, Ying G-S, et al. Photographic assessment of baseline fundus morphologic features in the Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology. 2012;119(8):1634–1641. doi:10.1016/j.ophtha.2012.02.013 [PubMed: 22512984]
12. Ying G-S, Maguire MG, Daniel E, et al. Association between Antiplatelet or Anticoagulant Drugs and Retinal or Subretinal Hemorrhage in the Comparison of Age-Related Macular Degeneration Treatments Trials. Ophthalmology. 2016;123(2):352–360. doi:10.1016/j.ophtha.2015.09.046 [PubMed: 26545320]
13. 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(9):1874–1885. doi:10.1016/j.ophtha.2012.03.014 [PubMed: 22705344]
14. Yu Y, Reynolds R, Rosner B, Daly MJ, Seddon JM. Prospective assessment of genetic effects on progression to different stages of age-related macular degeneration using multistate Markov

models. Invest Ophthalmol Vis Sci. 2012;53(3):1548–1556. doi:10.1167/iovs.11-8657 [PubMed: 22247473]

15. Syversen K Intramuscular iron therapy and tapetoretinal degeneration. A case report. Acta Ophthalmol (Copenh). 1979;57(3):358–361. [PubMed: 474082]
16. Cibis PA, Brown EB, Hong SM. Ocular effects of systemic siderosis. Am J Ophthalmol. 1957;44(4 Pt 2):158–172. [PubMed: 13469963]
17. Kennedy ET, Luo H, Houser RF. Dietary Supplement Use Pattern of U.S. Adult Population in the 2007–2008 National Health and Nutrition Examination Survey (NHANES). Ecol Food Nutr. 2013;52(1):76–84. doi:10.1080/03670244.2012.706000 [PubMed: 23282192]
18. Radimer K, Bindewald B, Hughes J, Ervin B, Swanson C, Picciano MF. Dietary Supplement Use by US Adults: Data from the National Health and Nutrition Examination Survey, 1999–2000. Am J Epidemiol. 2004;160(4):339–349. doi:10.1093/aje/kwh207 [PubMed: 15286019]
19. Dickinson A, Bonci L, Boyon N, Franco JC. Dietitians use and recommend dietary supplements: report of a survey. Nutr J. 2012;11(1):14. doi:10.1186/1475-2891-11-14 [PubMed: 22416673]
20. Dickinson A, Boyon N, Shao A. Physicians and nurses use and recommend dietary supplements: report of a survey. Nutr J. 2009;8(1):29. doi:10.1186/1475-2891-8-29 [PubMed: 19570197]
21. Zareparsi S, Branham KEH, Li M, et al. Strong association of the Y402H variant in complement factor H at 1q32 with susceptibility to age-related macular degeneration. Am J Hum Genet. 2005;77(1):149–153. doi:10.1086/431426 [PubMed: 15895326]
22. Edwards AO, Ritter R, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement Factor H Polymorphism and Age-Related Macular Degeneration. Science. 2005;308(5720):421–424. doi:10.1126/science.1110189 [PubMed: 15761121]
23. Haines JL, Hauser MA, Schmidt S, et al. Complement Factor H Variant Increases the Risk of Age-Related Macular Degeneration. Science. 2005;308(5720):419–421. doi:10.1126/science.1110359 [PubMed: 15761120]
24. Klein RJ, Zeiss C, Chew EY, et al. Complement Factor H Polymorphism in Age-Related Macular Degeneration. Science. 2005;308(5720):385–389. doi:10.1126/science.1109557 [PubMed: 15761122]
25. Maguire MG, Ying G-S, Jaffe GJ, et al. Single-Nucleotide Polymorphisms Associated With Age-Related Macular Degeneration and Lesion Phenotypes in the Comparison of Age-Related Macular Degeneration Treatments Trials. JAMA Ophthalmol. 2016;134(6):674–681. doi:10.1001/jamaophthalmol.2016.0669 [PubMed: 27099955]
26. Ueda Y, Mohammed I, Song D, et al. Murine systemic thrombophilia and hemolytic uremic syndrome from a factor H point mutation. Blood. 2017;129(9):1184–1196. doi:10.1182/blood-2016-07-728253 [PubMed: 28057640]
27. Li Y, Song D, Song Y, et al. Iron-induced Local Complement Component 3 (C3) Up-regulation via Non-canonical Transforming Growth Factor (TGF)-β Signaling in the Retinal Pigment Epithelium. J Biol Chem. 2015;290(19):11918–11934. doi:10.1074/jbc.M115.645903 [PubMed: 25802332]

Table 1

Comparison of baseline characteristics between participants with vs. without use of iron supplements (N=1165[*])

	Iron use at baseline		
Baseline characteristics	**No (N=984)**	**Yes (N=181)**	**P-value**
Age (years): Mean (SD)	79.0 (7.6)	80.2 (6.9)	0.04
Female (%)	609 (61.9%)	112 (61.9%)	1.00
Former or current cigarette smoker (%)	559 (56.8%)	106 (58.6%)	0.66
Taking AREDS supplement (%)	586 (59.6%)	150 (82.9%)	<0.0001
Presence of diabetes (%)	166 (16.9%)	37 (20.4%)	0.24
Presence of hypertension (%)	674 (68.5%)	128 (70.7%)	0.55
Systolic BP (mmHg): mean (SD)	135 (17.9)	133 (16.7)	0.09
Diastolic BP (mmHg): mean (SD)	76 (10.1)	75 (9.7)	0.59
History of cardiovascular diseases	217 (22.1%)	59 (32.6%)	0.002
Osteoarthritis	452 (45.9%)	95 (52.5%)	0.11
Rheumatoid arthritis	56 (5.7%)	13 (7.2%)	0.43
Anemia			<0.0001
None	834 (90.9%)	127 (70.2%)	
Past	42 (4.3%)	25 (13.8%)	
Ongoing	48 (4.9%)	29 (16.0%)	
Baseline use of antiplatelet or anticoagulant drug (%)	501 (50.9%)	107 (59.1%)	0.04
CNV in the fellow eye	296 (30.1%)	9 (27.1%)	0.42
Visual acuity in study eye: Mean (SD) in letters	60.4 (13.5)	60.9 (13.6)	0.61
Total area of CNV lesion (disc area): mean (SD)	2.5 (2.5)	2.3 (2.6)	0.29
Total retinal thickness (microns): mean (SD)	462 (189)	463 (178)	0.94

SD=Standard deviation, BP=blood pressure, CNV=Choroid neovascularization.

[*]Of 1185 CATT participants, 20 patients did not have good image quality images for determining retinal/subretinal hemorrhage, leaving 1165 participants for analysis.

[†]Adjusted by age, gender, smoking status, dietary supplement use, hypertension, diabetes, CVD history, use of antiplatelet or anticoagulant, and CNV in fellow eye.

Table 2:

Association of iron use with retinal or subretinal hemorrhage in the study eye of CATT participants at baseline among all participants and stratified by hypertension status

			Unadjusted analysis		Adjusted analysis†	
Iron use at baseline	**n**	**Hemorrhage (%)**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Among all CATT Participant (N=1165)						
Iron use				0.004		0.04
No	984	596 (60.6%)	1.00		1.00	
Yes	181	128 (70.7%)	1.57 (1.11 – 2.22)		1.47 (1.02 – 2.13)	
Iron dose				0.008*		0.048*
No iron use	984	596 (60.6%)	1.00		1.00	
<18 mg	40	26 (65.0%)	1.21 (0.62 – 2.34)	0.57	1.18 (0.60 – 2.35)	0.63
18–36 mg	87	53 (70.1%)	1.53 (0.95 – 2.46)	0.08	1.66 (1.01 – 2.73)	0.046
>36 mg	42	32 (76.2%)	2.08 (1.01 – 4.29)	0.046	1.38 (0.63 – 3.02)	0.42
Without hypertension at baseline (n=363)						
Iron use				0.76		0.68
No	310	190 (61.3%)	1.00		1.00	
Yes	53	34 (64.2%)	1.13 (0.62 – 2.07)		0.87 (0.44 – 1.72)	
Iron dose				0.61*		0.56*
No iron use	310	190 (61.3%)	1.00		1.00	
<18 mg	12	8 (66.7%)	1.26 (0.37 – 4.29)	0.71	1.11 (0.29 – 4.28)	0.88
18–36 mg	19	12 (63.2%)	1.08 (0.42 – 2.83)	0.87	1.24 (0.45 – 3.47)	0.68
>36 mg	18	12 (66.7%)	1.26 (0.46 – 3.46)	0.65	0.45 (0.12 – 1.68)	0.23
With hypertension at baseline (n=802)						
Iron use				0.005		0.006
No	674	406 (60.2%)	1.00			
Yes	128	94 (73.4%)	1.82 (1.20 – 2.78)		1.87 (1.19 – 2.92)	
Iron dose				0.005*		0.009*
No iron use	674	406 (60.2%)	1.00		1.00	

			Unadjusted analysis		Adjusted analysis†	
Iron use at baseline	**n**	**Hemorrhage (%)**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
<18 mg	28	18 (64.3%)	1.19 (0.54 – 2.61)	0.67	1.32 (0.59 – 2.99)	0.50
18–36 mg	68	49 (72.1%)	1.70 (0.98 – 2.96)	0.06	1.84 (1.03 – 3.28)	0.04
>36 mg	24	20 (83.3%)	3.30 (1.12 – 9.76)	0.03	2.65 (0.85 – 8.25)	0.09

OR=Odds ratio, CI=Confidence interval.

*From test of linear trend. No dose information is available for 12 patients (4 without hypertension, 8 with hypertension), they were excluded from the analysis of dose association.

†Adjusted by age, gender, smoking status, dietary supplement use, hypertension, diabetes, anemia, CVD history, use of antiplatelet or anticoagulant and CNV in fellow eye.

Table 3

Association of iron use with retinal or subretinal hemorrhage in the study eye of CATT participants at baseline among those without past history or ongoing anemia (n=1021)

			Unadjusted analysis		Adjusted analysis†	
Iron use at baseline	**n**	**Hemorrhage (%)**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
All subjects without anemia at baseline (n=1021)						
Iron use				0.15		0.09
No	894	532 (59.5%)	1.00		1.00	
Yes	127	84 (66.1%)	1.33 (0.90 – 1.97)		1.43 (0.95 – 2.14)	
Iron dose				0.12*		0.07*
No iron use	894	532 (59.5%)	1.00		1.00	
<18 mg	35	22 (62.9%)	1.15 (0.57 – 2.32)	0.69	1.16 (0.57 – 2.39)	0.68
18–36 mg	70	49 (70.0%)	1.59 (0.94 – 2.69)	0.09	1.89 (1.09 – 3.27)	0.02
>36 mg	13	7 (53.8%)	0.79 (0.27 – 2.38)	0.68	0.65 (0.21 – 2.00)	0.45
Without hypertension at baseline (n=323)						
Iron use				0.61		0.81
No	287	172 (59.9%)	1.00		1.00	
Yes	36	20 (55.6%)	0.83 (0.42 – 1.68)		0.86 (0.52 – 1.43)	
Iron dose				0.76*		0.91*
No iron use	287	172 (59.9%)	1.00		1.00	
<18 mg	10	6 (60.0%)	1.00 (0.28 – 3.63)	1.00	1.15 (0.29 – 4.60)	0.85
18–36 mg	18	12 (66.7%)	1.34 (0.49 – 3.66)	0.57	1.50 (0.52 – 4.38)	0.46
>36 mg	5	1 (20.0%)	0.17 (0.02 – 1.52)	0.11	0.16 (0.02 – 1.56)	0.12
With hypertension at baseline (n=698)						
Iron use				0.04		0.02
No	607	360 (59.3%)	1.00		1.00	
Yes	91	64 (70.3%)	1.63 (1.01 – 2.62)		1.85 (1.12 – 3.05)	
Iron dose				0.06*		0.02*

Retina. Author manuscript; available in PMC 2020 October 01.

			Unadjusted analysis		Adjusted analysis†	
Iron use at baseline	**n**	**Hemorrhage (%)**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
Not use iron	607	360 (59.3%)	1.00		1.00	
<18 mg	25	16 (64.0%)	1.22 (0.53 – 2.80)	0.64	1.36 (0.58 – 3.22)	0.48
18–36 mg	52	37 (71.2%)	1.69 (0.91 – 3.15)	0.10	2.05 (1.07 – 3.92)	0.03
>36 mg	8	6 (75.0%)	2.06 (0.41 – 10.3)	0.38	1.86 (0.36 – 9.73)	0.46

OR= odds ratio; CI= confidence interval.

*From test of linear trend. No dose information is available for 9 patients (3 without hypertension, 6 with hypertension), they were excluded from the analysis of dose association.

†Adjusted by age, gender, smoking status, dietary supplement use, hypertension, diabetes, CVD history, use of antiplatelet or anticoagulant, and CNV in fellow eye.

Table 4

Association of iron use with retinal or subretinal hemorrhage in the study eye of CATT participants at baseline

-Stratified by CFH genotype							
				Unadjusted analysis		Adjusted analysis†	
Iron use at baseline	**n**	**Hemorrhage (%)**	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
CFH=CC (C is risk allele for CFH)							
Iron use			0.04		0.04		0.07
No	225	136 (60.4%)		1.00		1.00	
Yes	40	31 (77.5%)		2.25 (1.02 – 4.96)		2.17 (0.94 – 5.01)	
CFH=TC							
Iron use			0.22		0.22		0.38
No	329	191 (58.1%)		1.00		1.00	
Yes	57	38 (66.7%)		1.45 (0.80 – 2.61)		1.34 (0.69 – 2.61)	
CFH=TT							
Iron use			0.93		0.93		0.67
No	139	93 (66.9%)		1.00		1.00	
Yes	31	21 (67.7%)		1.04 (0.45 – 2.39)		1.28 (0.47 – 3.18)	

OR= odds ratio; CI= confidence interval.

†Adjusted by age, gender, smoking status, dietary supplement use, hypertension, diabetes, anemia, CVD history, use of antiplatelet or anticoagulant, and CNV in fellow eye.

Table 5

The association between iron use with size of retinal/subretinal hemorrhage

		Size of retinal/subretinal hemorrhage at baseline				Linear trend P-value
Iron use at baseline	**N**	**No hemorrhage (n=441)**	**≤ 1 DA (n=611)**	**>1, ≤ 2 DA (n=59)**	**> 2 DA (n=54)**	
Iron use						0.01
No	984	388 (39.4%)	506 (51.4%)	47 (4.8%)	43 (4.4%)	
Yes	181	53 (29.3%)	105 (58.0%)	12 (6.6%)	11 (6.1%)	
Iron dose*						0.007
No iron use	984	388 (39.4%)	506 (51.4%)	47 (4.8%)	43 (4.4%)	
<18 mg	40	14 (35.0%)	22 (55.0%)	0 (0.0%)	4 (10.0%)	
18–36 mg	87	26 (29.9%)	49 (56.3%)	6 (6.9%)	6 (6.9%)	
>36 mg	42	10 (23.8%)	26 (61.9%)	5 (11.9%)	1 (2.4%)	

DA = Disc area.

* No dose information is available for 12 patients; they were excluded from the analysis of dose association.