Compliance with ethical standards

Conflict of interest A.S. is an Innovator of MII Ret Cam. None of the other authors have the conflict of interest with this submission

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The effect of statin exposure on choroidal neovascularization in nonexudative age-related macular degeneration patients

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Age-related macular degeneration (AMD) is the leading cause of blindness above age 65 in industrialized countries [1]. While early-stage (nonexudative) AMD is characterized by drusenoid deposits that typically do not affect vision, late-stage AMD consists of geographic atrophy (GA) or choroidal neovascularization (CNV, also known as exudative AMD) which can cause significant vision loss.

While antioxidant AREDS vitamins are currently most commonly prescribed for nonexudative AMD, no standard treatment has been established [2]. However, AMD shares several risk factors with atherosclerosis and may have similar pathophysiology [1]. Therefore, statins (β-hydroxy β-methylglutaryl-CoA [HMG-CoA] reductase inhibitors) have been hypothesized as a potential treatment. Research thus far on this topic has been contradictory. CNV in particular is not well understood with fewer relevant trials and observational studies [3, 4]. In a recent prospective cohort of 26 patients on high-dose atorvastatin (80 mg), 10 showed drusen regression, while none progressed to CNV [4]. Large-scale retrospective studies are needed to investigate this further, a gap our study addresses.

Using the Stanford University Medical Center (SUMC) Clinical Data Warehouse, we performed a cross-sectional study of patients with nonexudative AMD seen at SUMC since 2008. Subjects were identified using ICD-9/ICD-10 codes 362.51/H35.31. The influence of statin exposure and covariates age, gender, race, and presence of comorbidities (ICD-9/ICD-10 codes for hypercholesterolemia, hypertension, cardiovascular disease, or cerebrovascular disease) on development of CNV (ICD-9/ICD-10 362.52/H35.32) were examined using crude bivariate analyses (chi-squared) and multivariate logistic regression. Statistical assumptions were met. The protocol was approved by the Stanford University Institutional Review Board.

The study population included 3090 patients (Table 1). Approximately half (49.7%) were on statins and 26.3% developed CNV. Those on statins tended to be older (67.8% ≥80), White (77.5%), and have more comorbidities (84.4%). A larger proportion of statin users developed CNV (29.3%) compared to non-statin users (23.3%). Multivariate logistic regression analysis adjusting for age, sex, race, and comorbidity status revealed statin users have increased odds of CNV (OR 1.27, CI 1.06–1.51) (Table 2). Subjects aged

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Table 1 Demographics of nonexudative age-related macular degeneration patients by statin exposure

Characteristic		All patients ($n = 3090$) n (%)	Statins ($n = 1535$) n (%)	No statins ($n = 1555$) n (%)	p-value
Age					
	<80	1105(35.8)	495(32.2)	610(39.2)	<0.0001
	≥80	1985(64.2)	1040(67.8)	945(60.8)	
Sex					
	Female	1905(61.7)	840(54.7)	1065(68.5)	<0.0001
	Male	1185(38.3)	695(45.3)	490(31.5)	
Race					
	White	2320(75.1)	1190(77.5)	1130(72.7)	0.0018
	Non-White	770(24.9)	345(22.5)	425(27.3)	
Comorbid conditions					
	None	1035(33.5)	240(15.6)	795(51.1)	<0.0001
	Hypercholesterolemia				
	Hypertension				
	Cardiovascular disease				
	Cerebrovascular disease	2055(66.5)	1295(84.4)	760(48.9)	
Statin use					
	No statins	1555(50.3)	–	–	
	Statins	1535(49.7)	–	–	
CNV					
	No CNV	2278(73.7)	1085(70.7)	1193(76.7)	0.0001
	CNV	812(26.3)	450(29.3)	362(23.3)	

CNV choroidal neovascularization

Table 2 Characteristics associated with choroidal neovascularization in nonexudative age-related macular degeneration patients

Characteristic		Unadjusted		Adjusted	
		Odds ratio	95% CI	Odds ratio	95% CI
Age					
	<80	1.00 [Reference]		1.00 [Reference]	
	≥80	2.97	2.45 to 3.61	2.82	2.32 to 3.44
Sex					
	Female	1.00 [Reference]		1.00 [Reference]	
	Male	0.87	0.74 to 1.03	0.85	0.71 to 1.01
Race					
	White	1.00 [Reference]		1.00 [Reference]	
	Non-White	0.47	0.38 to 0.58	0.50	0.40 to 0.61
Statin use					
	No statins	1.00 [Reference]		1.00 [Reference]	
	Statins	1.37	1.16 to 1.61	1.27	1.06 to 1.51
Comorbid conditions					
	None	1.00 [Reference]		1.00 [Reference]	
	Hypercholesterolemia				
	Hypertension				
	Cardiovascular disease				
	Cerebrovascular disease	1.38	1.16 to 1.65	1.02	0.84 to 1.25

≥80 (OR 2.82, CI 2.32–3.44) and White (Reference Non-White: OR 0.50, CI 0.40–0.61) were also more likely to develop CNV after controlling for covariates. Interestingly, comorbidity effects disappeared after multivariate adjustment (OR 1.02, CI 0.84–1.25).

This cross-sectional study adds to the growing literature around the therapeutic potential of statins in preventing AMD progression. Advanced AMD prevalence estimates for GA vs. CNV range from 1:1 to 2:1; however, GA currently has no treatment [5]. As suggested by Miller et al. statins may allow for drusen regression potentially circumventing GA [4]. Therefore, if statins are associated with CNV as indicated in our study, this is a small exchange given vision can be well preserved in these patients with existing therapies like anti-VEGF (vascular endothelial growth factor) [1]. Our study is a preliminary exploration of statin effect on CNV. The observed association is likely complicated by treatment and risk factors unavailable in our database and could be subject to residual confounding. Large cohort studies and

randomized controlled trials incorporating risk and treatment factors (dose, class, course length, hydrophilicity) are necessary [4]. In conclusion, given the global disease burden and grave implications of advanced AMD, novel treatment with statins deserves further study and consideration.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Van gogh and the obsession of yellow: style or side effect

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Vincent Van Gogh is well known for his yellow addiction, which might be related to a health condition [1]. There are several theories about his possible diseases, including epilepsy, Meniere's disease, and acute intermittent porphyria [2–6].

This yellow obsession makes professionals wonder: were those only reflection of his mind or how he saw the world?

There are different theories around this however, this hypothesis will focus on one theory: *Xanthopsia*. Xanthopsia is a rare condition that causes yellow vision which can also occur due to medications. Digitalis rarely causes yellow vision following bilirubin deposition in the eye which possibly explains his yellow addiction according to some specialists [7–9]. It is well known that he was treated by the famous physician Paul Gachet during the 19th century (Fig. 1). During that time foxglove plant, which is the main ingredient of digitalis, was used for the treatment of epilepsy and mania [2, 10–13].

Although, we don't have the medical recordings of him, it is possible that Gachet used digoxin on him considering Gogh painted him several times with foxglove plants [2, 14, 15].

Moreover, the yellow color dominates his paintings he painted during his hospital stay.

Although there are several reasons to consider this yellow love is not natural, the opposite seems more reliable because of several reasons.

First, his treatment under Gachet lasted only 2 months. Studies suggest 2 months are not enough for the development of xanthopsia [16].

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