JNS

CLINICAL ARTICLE

J Neurosurg 142:1366–1375, 2025

The association of statin therapy with reduced intracranial aneurysm recurrence after endovascular coiling: a post hoc propensity score–matched analysis of a randomized clinical trial

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OBJECTIVE Endovascular intracranial aneurysm (IA) management has significantly evolved over the last 2 decades. Despite these advancements, the aneurysm recanalization rate after coil embolization remains a concern. Statins have been found to affect vascular repair and remodeling; therefore, the authors hypothesized that patients receiving statin therapy at the time of coil embolization would have lower aneurysm recurrence and retreatment rates compared with patients not receiving statin therapy.

METHODS A post hoc analysis was conducted of the primary data from patients enrolled in the Hydrogel Endovascular Aneurysm Treatment Trial focusing on the impact of statin use on the recurrence rates of 3- to 14-mm IAs after endovascular coiling. The primary outcome measured included aneurysm recurrence over 18–24 months using the Raymond-Roy Occlusion Classification. Secondary outcomes included major and minor recurrence rates and retreatment rates. Propensity score matching based on patient and aneurysm characteristics was performed to mitigate selection bias.

RESULTS A total of 577 patients with data on statin use were eligible for this analysis. Of these, 178 (30.8%) patients were using statins and 399 (69.2%) were not. After propensity score matching, 156 (39.2%) patients were included in the statin group and 242 (60.8%) in the nonstatin group. The recurrence rate was 3.8% (6/156) in the statin group and 10.7% (26/242) in the nonstatin group ($p = 0.013$). In a subgroup analysis, statin use significantly reduced recurrence in patients with unruptured aneurysms (1.6% vs 9.7%, $p = 0.005$), but not in those with ruptured aneurysms (12.5% vs 13.6%, $p = 0.876$).

CONCLUSIONS Statin use was associated with a reduced rate of aneurysm recurrence in patients who underwent endovascular coiling for IAs with a decreased rate of retreatment during the follow-up period. Statins are a relatively low-risk treatment and may be an effective therapy to reduce recanalization of IAs, although further prospective studies are warranted to validate these findings.

https://thejns.org/doi/abs/10.3171/2024.7.JNS24781

KEYWORDS intracranial aneurysm; endovascular procedures; HMG-CoA reductase inhibitor; propensity score; endovascular neurosurgery; vascular disorders

Endovascular intracranial aneurysm (IA) management has evolved dramatically in the last 2 decades. Several treatment options exist, including endovascular coiling with or without balloon or stent assistance, flow diversion, or flow disruption for varying aneurysm morphologies and complexities. Significant advancements have been made in the last 2 decades to increase the safety and efficacy of aneurysm treatment; however, the durabil-

ABBREVIATIONS BPC = bare platinum coil; HEAT = Hydrogel Endovascular Aneurysm Treatment Trial; HES = HydroCoil Embolic System; IA = intracranial aneurysm.

SUBMITTED March 30, 2024. **ACCEPTED** July 29, 2024.
INCLUDE WHEN CITING Published online December 20, 2024; DOI: 10.3171/2024.7.JNS24781.

ity of aneurysm occlusion with coil embolization remains a concern, with an estimated recanalization rate of 20% and approximately one-half requiring retreatment.[1,2] Multiple factors have been evaluated with the development of a stratification scale to predict aneurysm recanalization, including both aneurysm-specific and treatment-related factors.[3,4] Several strategies, such as improving packing density using balloon/stent assistance and using surface-modified coils like poly(lactic-co-glycolic acid) coils and hydrocoils, have been attempted to reduce recanalization. A recent randomized controlled trial comparing bare platinum coils (BPCs) and second-generation hydrocoils in the coiling of small- to medium-sized aneurysms showed reduced recurrence rates with the use of hydrocoils.[5] The low recurrence rate with hydrocoils was attributed to improved packing density and biological healing, both within the aneurysm and at the neck. Several studies using animals and tissue models have demonstrated the important role of inflammation and endothelial repair in the process of aneurysm healing.[6,7] Therefore, considerable research efforts are underway to investigate and develop therapeutic agents targeting the inflammatory healing cascade. Statins are agents that have been used for several health benefits, including reducing cardiovascular and cerebrovascular risks by inhibiting a proinflammatory cascade. The beneficial effect of statins has also been shown in aortic aneurysms.[8,9] Statins have been shown to affect vascular repair and remodeling through both angiogenic and angiostatic mechanisms promoting aneurysm healing.[6] Additionally, animal studies have demonstrated an increased rate of aneurysm neck endothelialization with the use of rosuvastatin after aneurysm coiling by promoting circulating endothelial progenitor cells.[7] The benefit of statin use has been shown in one clinical study on IAs after endovascular coiling.[10] However, further validation is lacking in larger studies. In this study, the authors performed a post hoc analysis of the Hydrogel Endovascular Aneurysm Treatment Trial (HEAT),[5] which is a randomized controlled trial involving the endovascular coiling of small- to medium-sized IAs, to analyze the effect of statin treatment on aneurysm recurrence rate.

Methods

The HEAT study is a prospective investigator-initiated randomized trial that compared the HydroCoil Embolic System (HES) (MicroVention Inc.) with BPCs in the endovascular treatment of 3- to 14-mm ruptured and unruptured aneurysms across 46 sites in the United States and Canada.[5] In the current study, we performed a post hoc analysis of the primary data collected for the patients enrolled in the HEAT study to analyze the effect of statin use (a group of medications including atorvastatin, simvastatin, rosuvastatin, and pravastatin) on aneurysm recurrence rates in the follow-up period.

Baseline Characteristics

The primary data that were collected for this analysis included patient demographics (age, sex, ethnicity, and race), aneurysm characteristics (rupture status, location, type, diameter, shape, and dome-to-neck ratio), patient characteristics (family history of aneurysm, smoking, alcohol use, diabetes, hypertension, obesity, and aspirin use), and primary procedure details (coiling method; use of an assisted device like a stent, balloon, or both; and extent of aneurysm occlusion at the initial procedure). The factors comprising each category are shown in Table 1. The baseline outcomes were compared between patients who used statins and those who did not. To note, the patients who were on statins at baseline continued their medication as advised by their primary care physician or cardiologist for the prevention or treatment of cardiovascular risk rather than as a preventive strategy for aneurysm recurrence.

Outcome Analysis

The primary outcome that was analyzed was aneurysm recurrence over a follow-up period of 18–24 months, which was defined in the HEAT study as any progression on the Raymond-Roy Occlusion Classification (RROC) scale.[26] The secondary outcomes included major recurrence (defined as an increase on the RROC scale from class 1 to class 3, an increase from class 2 to class 3, or class 3 with an increase in the Meyer scale score), minor recurrence (defined as increase on the RROC scale from class 1 to class 2), and retreatment rate for recurrence.

Propensity Score Matching

Propensity score matching was performed to reduce the selection bias from confounding factors. A balanced cohort was prepared based on the propensity scores generated using matching factors based on patient demographics, aneurysm and patient characteristics, and primary procedure details as mentioned above. The propensity scores allowed us to estimate the probability that a patient was exposed to a factor of interest (use of statins). A matched cohort was created by matching the propensity scores based on the kernel method, which allowed matching of multiple controls (no statin) to one patient (statin). The standardized bias across the probable confounding factors was compared pre- and postmatching to confirm satisfactory reduction of bias to an acceptable limit (defined as $< 5\%$). A logistic regression of the matched sample was performed to compare the primary and secondary outcomes between the patients who were statin users and nonusers.

Statistical Analysis

The analysis was performed using Stata statistical software version 18.0 (StataCorp LLC). The continuous variables are reported as mean and standard deviation. The binary/categorical variables are reported as frequency (percentage). The Pearson chi-square test was used for comparison of categorical variables, and the Student t-test was used for continuous variables. Logistic regression results are reported as odds ratio with 95% confidence interval. Both univariate and multivariate logistic regression analyses were performed. The univariate analysis included all the variables used for propensity score matching, but multivariate analysis included only the variables that had a p value significance level ≤ 0.1. Propensity score matching was performed using the kernel matching method after logit estimation without bandwidth using a common sup-

TABLE 1. Demographics of patients with or without statin use

	Unmatched Sample (n = 577)			Matched Sample (n = 398)		
	No Statin	Statin	p Value	No Statin	Statin	p Value
Mean age, yrs	54.8	61.8	<0.001	56	61	<0.001
Sex						
Male	84 (71.2)	34 (28.8)	0.591	42 (58.3)	30 (41.7)	0.635
Female	315 (68.6)	144 (31.4)		200 (61.3)	126 (38.7)	
Ethnicity						
Non-Hispanic	368 (69.8)	159 (30.2)	0.252	220 (61.5)	138 (38.5)	0.428
Hispanic	31 (62.0)	19 (38.0)		22 (55.0)	18 (45.0)	
Race						
White	316 (67.4)	153 (32.6)		194 (59.5)	132 (40.5)	
Black	47 (79.7)	12 (20.3)	0.270	29 (70.7)	12 (29.3)	0.716
Asian	14 (70.0)	6 (30.0)		9 (64.3)	5 (35.7)	
Other	14 (82.4)	3 (17.6)		5 (62.5)	3 (37.5)	
Rupture status						
Unruptured	275 (65.8)	143 (34.2)	0.005	176 (58.7)	124 (41.3)	0.126
Ruptured	123 (77.8)	35 (22.2)		66 (67.3)	32 (32.7)	
Aneurysm location						
Anterior circulation	336 (69.6)	147 (30.4)	0.415	204 (60.9)	131 (39.1)	0.931
Posterior circulation	50 (64.9)	27 (35.1)		38 (60.3)	25 (39.7)	
Aneurysm type						
Sidewall	135 (71.4)	54 (28.6)	0.573	81 (62.8)	48 (37.2)	0.837
Terminal	55 (65.5)	29 (34.5)		42 (60.9)	27 (39.1)	
Bifurcation	196 (68.1)	92 (31.9)		119 (59.5)	81 (40.5)	
Aneurysm diameter						
<7 mm	231 (67.7)	110 (32.3)	0.378	132 (58.7)	93 (41.3)	0.319
≥7 mm	168 (71.2)	68 (28.8)		110 (63.6)	63 (36.4)	
Aneurysm shape						
Regular	215 (65.7)	112 (34.3)	0.051	136 (58.6)	96 (41.4)	0.249
Irregular	85 (68.5)	39 (31.5)		56 (59.6)	38 (40.4)	
Daughter sac	86 (78.2)	24 (21.8)		50 (69.4)	22 (30.6)	
Dome-to-neck ratio						
≤1.5	32 (60.4)	21 (39.6)	0.165	21 (55.3)	17 (44.7)	0.462
>1.5	347 (69.7)	151 (30.3)		221 (61.4)	139 (38.6)	
Family history of aneurysm						
No family history	302 (69.3)	134 (30.7)	0.916	178 (61.0)	114 (39.0)	0.916
Family history	97 (68.8)	44 (31.2)		64 (60.4)	42 (39.6)	
History of smoking						
Never smoker	104 (68.4)	48 (31.6)	0.820	62 (62.0)	38 (38.0)	0.777
Ever smoker	295 (69.4)	130 (30.6)		180 (60.4)	118 (39.6)	
Aspirin use						
No aspirin	230 (80.4)	56 (19.6)	<0.001	125 (70.6)	52 (29.4)	<0.001
Aspirin	169 (58.1)	122 (41.9)		117 (52.9)	104 (47.1)	
Hypertension						
No	75 (65.2)	40 (34.8)	0.115	70 (66.0)	36 (34.0)	0.198
Yes	180 (56.8)	137 (43.2)		172 (58.9)	120 (41.1)	
Diabetes mellitus						
No	210 (61.2)	133 (38.8)	0.068	198 (62.7)	118 (37.3)	0.137
Yes	45 (50.6)	44 (49.4)		44 (53.7)	38 (46.3)	
Alcohol use						
No	358 (68.5)	165 (31.5)	0.258	224 (60.7)	145 (39.3)	0.885
Yes	41 (75.9)	13 (24.1)		18 (62.1)	11 (37.9)	
Obesity						
No	149 (75.6)	48 (24.4)	0.015	74 (62.7)	44 (37.3)	0.613
Yes: BMI ≥25	250 (65.8)	130 (34.2)		168 (60.0)	112 (40.0)	

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TABLE 1. Demographics of patients with or without statin use

	Unmatched Sample (n = 577)			Matched Sample (n = 398)		
	No Statin	Statin	p Value	No Statin	Statin	p Value
Coiling method						
BPCs	213 (72.7)	80 (27.3)	0.061	127 (64.1)	71 (35.9)	0.175
Hydrogel coils	186 (65.5)	98 (34.5)		115 (57.5)	85 (42.5)	
Use of stent						
No stent or balloon	137 (69.9)	59 (30.1)		90 (62.5)	54 (37.5)	
Balloon	166 (71.6)	66 (28.4)	0.231	99 (61.9)	61 (38.1)	0.640
Stent	80 (66.1)	41 (33.9)		47 (58.0)	34 (42.0)	
Balloon & stent	9 (50.0)	9 (50.0)		6 (46.2)	7 (53.8)	
Aneurysm occlusion at initial procedure						
Complete	81 (64.8)	44 (35.2)		42 (53.8)	36 (46.2)	
≥90%	178 (73.0)	66 (27.0)		118 (65.6)	62 (34.4)	
70–89%	77 (65.3)	41 (34.7)	0.522	50 (57.5)	37 (42.5)	0.412
50–69%	34 (66.7)	17 (33.3)		24 (58.5)	17 (41.5)	
25–49%	10 (71.4)	4 (28.6)		8 (66.7)	4 (33.3)	
<25%	1 (100)	0 (0)		0 (0)	0 (0)	

Values are given as number of patients (%) unless otherwise indicated.

port. The caliper option was set at 0.02. Graphical representation of the matching was performed using a scatter diagram and kernel density plots. A p value < 0.05 was set as the threshold for statistical significance.

Results

A total of 600 patients were enrolled in the original HEAT study, of whom 577 patients were eligible for this post hoc analysis due to having data on statin use. A total of 178 (30.8%) patients were on statin therapy at baseline that was continued in the postoperative period. The baseline characteristics of the patients in the original cohort in the two groups (statin users and nonusers) are described in Table 1.

Matching Outcome

After matching patients based on propensity scores, 398 patients, 156 (39.2%) statin users and 242 (60.8%) nonusers, were included in the matched cohort. The difference between the two groups in all the variables was not statistically significant in the matched cohort except for mean age and aspirin use (Table 1). The mean bias in the matched cohort was 2.5% as compared with 13.8% in the unmatched cohort, suggesting a reduction of bias by > 80% with matching. The balancing test of all variables in the matched cohort showed a bias of < 5% in all the variables, confirming the comparability of the groups (Table 2). The scatter diagram showing the standardized percent bias in the unmatched and matched samples for each variable is depicted in Fig. 1. The kernel density plot shows a satisfactory balance between the groups in the matched cohort (Fig. 2).

Baseline Characteristics in the Matched Cohort

The matched cohort consisted of 98 (24.6%) patients

TABLE 2. Balance test depicting percent bias before and after matching

	% Bias			
	Before Matching	After Matching	% Change	p Value (matched group)
Age	61.0	4.6	92.4	0.65
Sex	−6.2	−3.6	42.3	0.75
Ethnicity	7.5	2.1	71.7	0.85
Race	−6.6	−0.3	96.1	0.98
Rupture status	−16.2	1.8	89.0	0.86
Aneurysm location	−0.4	−1.9	−412.7	0.87
Aneurysm type	5.9	3.0	49.2	0.79
Aneurysm diameter	−12.0	0.8	93.4	0.94
Aneurysm shape	−20.2	3.7	81.8	0.73
Dome-to-neck ratio	−10.8	4.4	59.1	0.71
Family history of aneurysm	−1.6	4.0	−149.7	0.72
History of smoking	2.5	0.1	96.6	0.99
Aspirin use	41.1	−2.9	92.8	0.78
Hypertension	15.5	3.1	80.3	0.78
Diabetes mellitus	18.3	−4.0	78.4	0.74
Alcohol use	−3.3	1.3	60.9	0.90
Obesity	8.0	−2.6	67.2	0.81
Coiling method	18.8	3.1	83.3	0.78
Use of stent	13.8	−1.1	91.9	0.92
Aneurysm occlusion at initial procedure	−6.7	1.6	75.6	0.88

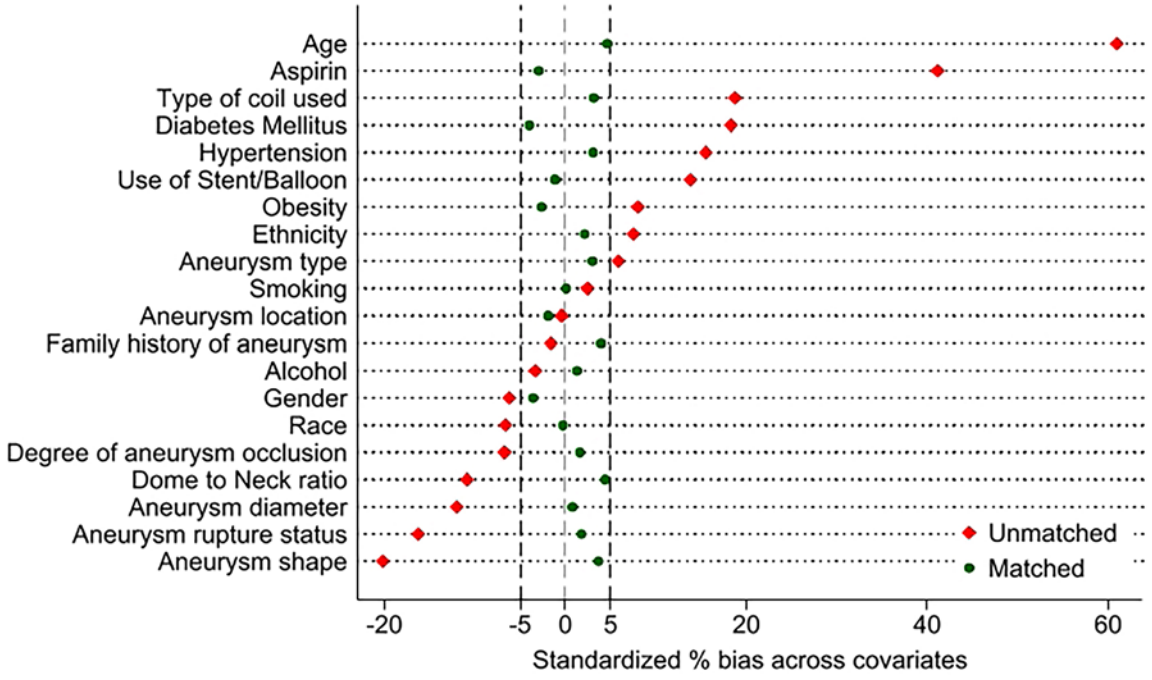

FIG. 1. Scatter diagram showing standardized percent bias in the unmatched and matched samples for each variable. Figure is available in color online only.

with ruptured aneurysms. About one-half (43.5%) of the patients had large aneurysms (≥ 7 mm in diameter). The aneurysm was regular in 58.3% of the patients and was irregular or had a daughter sac in 41.7%. About 16.6% of the patients had a family history of aneurysm in first-degree relatives and 10% in second-degree relatives. About three-quarters (74.9%) of the patients had a history of smoking. The rate of comorbidities in the cohort included hypertension in 73.4%, diabetes mellitus in 20.6%, and obesity (BMI ≥ 25) in 70.4% of patients. About one-half (50.3%) of the patients had endovascular coiling using second-generation hydrocoils (at least 90% of the total implanted coil length). Assisted devices (balloon, stent, or both) were used for coiling in 63.8% of patients. The rates of complete occlusion, ≥ 90% occlusion, and ≥ 70% occlusion were 19.6%, 64.8%, and 86.7%, respectively (Table 1).

Primary Outcome Analysis

A total of 32 (8.0%) patients experienced a recurrence in the matched cohort. In the statin group, 6 (3.8%) recurrences were observed, compared with 26 (10.7%) recurrences in the group without statin use (p = 0.013) (Fig. 3). The logistic regression showed a lower odds of recurrence in the statin group (OR 0.33, 95% CI 0.13–0.82; p = 0.018) (Fig. 4).

Secondary Outcome Analysis

The rate of major and minor recurrences in the matched cohort were 11.8% and 2.2%, respectively. The overall rate of major recurrence was lower in the statin group (7.6% vs 14.4%, p = 0.041). Similarly, the odds of major recurrence was lower in the statin user group compared with the group of statin nonusers (OR 0.49, 95% CI 0.24–0.98; p = 0.044). The rate of minor recurrence was also lower in the statin group, but not statistically significant between the groups (1.9% with statins vs 2.4% without statins, p = 0.71; OR 0.77, 95% CI 0.19–3.12 [p = 0.716]). Similarly, the rate of retreatment in the statin group was lower without reaching significance (2.6% with statins vs 4.1% without statins, p = 0.40; OR 0.61, 95% CI 0.18–1.98 [p = 0.41]) (Figs. 3 and 4).

Factor and Subgroup Analysis

Univariate analysis of the factors in the matched sample was performed and showed rupture status, coiling method, and aneurysm occlusion at the initial procedure as significant factors affecting aneurysm recurrence in addition to statin use (Table 3). The multivariate analysis showed lower odds of recurrence with the use of statins (OR 0.29, 95% CI 0.11–0.77; p = 0.013), use of HES coils (OR 0.26, 95% CI 0.10–0.69; p = 0.007), and aneurysm occlusion > 90% at the time of the initial procedure (OR 0.38, 95% CI 0.16–0.85; p = 0.019). In the subgroup analysis based on rupture status, significantly lower recurrence was noted with statin use in patients' unruptured aneurysms (1.6% vs 9.7%, p = 0.005); however, the difference was not significant in patients with ruptured aneurysms (12.5% vs 13.6%, p = 0.876). Similarly, in the subgroup analysis based on type of coil used, a significantly lower recurrence was noted in patients with the use of HES coils and statins (0.0% vs 5.2%, p = 0.032); however, the difference was not significant in patients undergoing coiling with BPCs (8.5% vs 15.8%, p = 0.145).

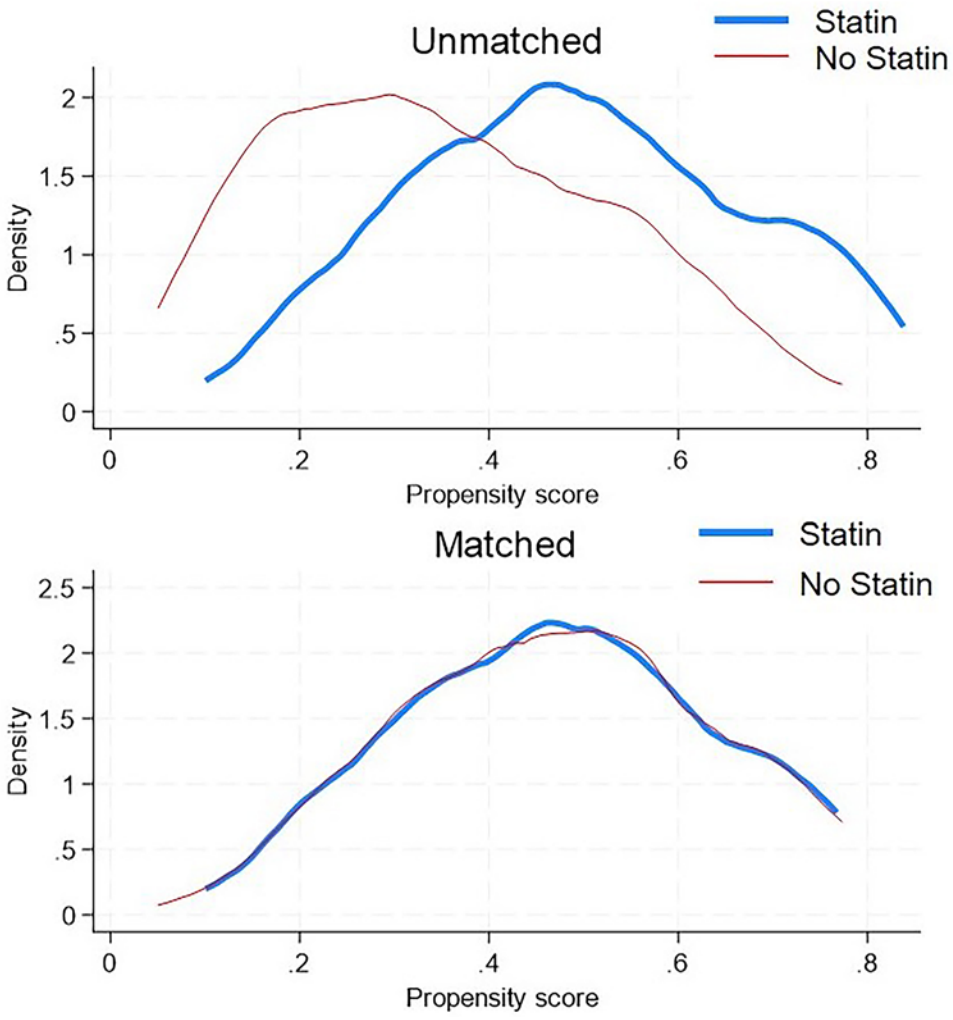

FIG. 2. Kernel density plot showing a satisfactory balance between the groups in the matched cohort. Figure is available in color online only.

Discussion

Our post hoc analysis of a large prospective randomized study demonstrated a beneficial effect on aneurysm recurrence with the use of statins after endovascular coiling. In the matched sample, patients who were on a statin had a 50% reduction in the rate of recurrence compared with patients who were not on a statin. This reduction also led to a trend toward a lower retreatment rate in the statin patient cohort.

Statins have been in use for the last several decades in the cardiovascular field, and current guidelines strongly recommend intense statin therapy in patients with significant atherosclerotic cardiovascular disease. In addition to its lipid-lowering properties, several other pathophysiological effects of statins have been implicated in promoting vascular health. Oxidative stress has been shown to increase the inflammatory cascade through the upregulation of cytokines and adhesion molecules, which lead to endothelial injury and the formation and growth of aneurysms. The use of statins tends to counteract these effects by enhancing nitric oxide production from the endothelium and reducing the generation of reactive oxygen species.[11] Additionally, statins have been shown to reduce the level of matrix metalloproteinases, which are known to mediate vascular remodeling and plaque rupture.[12] Statins also decrease other inflammatory markers like interleukin-6, C-reactive protein, and tumor necrosis factor–alpha.[13]

Similar to the pathomechanism of systemic atherosclerosis, intimal thickening and smooth muscle proliferation in intracranial vasculature have been implicated in the formation, growth, and rupture of cerebral aneurysms.[14] Limited data exist on the effects of statin on IAs, but studies have shown beneficial effects of statin on both ruptured and unruptured aneurysms. A multicenter study from Japan analyzing the data in 117 patients with ruptured aneurysms and 304 patients with unruptured aneurysms found a lower odds of hemorrhage in patients using statins (adjusted OR 0.3, 95% CI 0.14–0.66).[15] Similarly, a case-control study on Medicare patients with IAs showed that statin use was associated with a lower risk of rupture and out-of-hospital death.[16] Later, Song et al. analyzed 1381 pa-

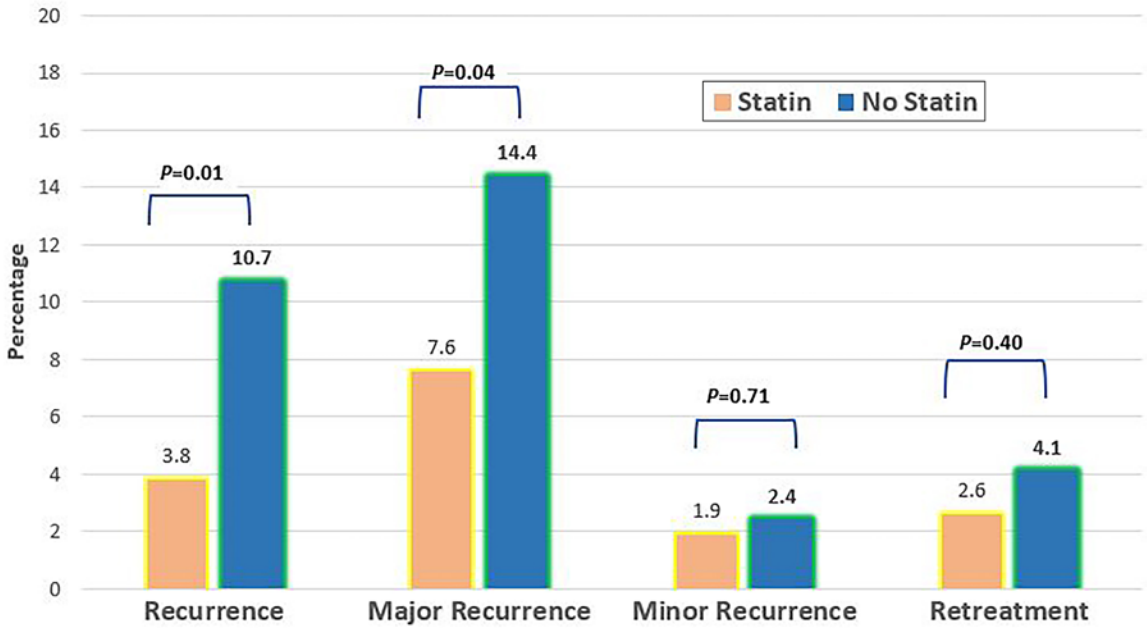

FIG. 3. Bar graph showing primary and secondary outcomes with or without statin use. Figure is available in color online only.

tients from the national database of Korea, including 542 patients undergoing endovascular embolization and 839 patients undergoing microsurgical clipping, and evaluated the role of statin use in the development of a composite outcome consisting of stroke, myocardial infarction, and all-cause death.[17] They demonstrated that consistent statin use, defined as use for > 80% of the days, is associated with a lower risk of the composite outcome.

In addition to reducing the risk of aneurysm rupture, statins have been proposed to promote aneurysm healing after treatment. One initial experiment on rodents showed that rosuvastatin promotes endothelialization of the coiled aneurysm neck by inducing endothelial progenitor cells and therefore can potentially be used as a target agent to prevent aneurysm recurrence.[7] Unfortunately, a subsequent study in rabbits in which simvastatin was used failed

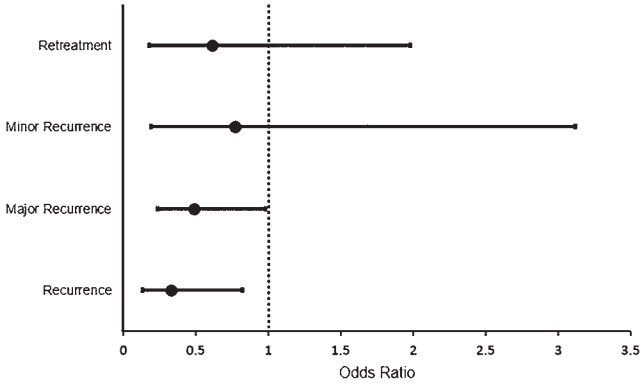

FIG. 4. Forest plot showing the odds of primary and secondary outcomes with statin use.

TABLE 3. Univariate and multivariate analyses of factors affecting aneurysm recurrence

	Univariate Analysis		Multivariate Analysis	
	OR	p Value	OR	p Value
Age	0.98	0.368		
Sex	0.77	0.563		
Ethnicity	1.75	0.280		
Race	1.18	0.354		
Rupture status	2.26	0.032	1.81	0.152
Aneurysm location	1.25	0.638		
Aneurysm type	1.01	0.952		
Aneurysm diameter	1.33	0.438		
Aneurysm shape	1.29	0.250		
Dome-to-neck ratio	1.63	0.512		
Family history of aneurysm	0.61	0.297		
History of smoking	0.84	0.684		
Aspirin use	0.90	0.776		
Statin	0.33	0.018	0.29	0.013
Hypertension	1.09	0.828		
Diabetes mellitus	0.37	0.114		
Alcohol use	0.38	0.362		
Obesity	0.92	0.836		
Coiling method	0.20	0.001	0.26	0.007
Use of stent	0.68	0.121		
Aneurysm occlusion at initial procedure	0.24	<0.001	0.38	0.019

to show a difference in healing of experimental aneurysms after BPC embolization.[18] The equivocal result of this study was thought to be related to the difference in animal models and use of a less potent statin (simvastatin as compared with rosuvastatin). Nevertheless, a subsequent clinical study by the same group analyzed the effect of statins on ruptured aneurysms ≤ 10 mm and found a significantly lower aneurysm recanalization rate with the use of statins.[10]

Our study, which included both ruptured and unruptured aneurysms, showed similar results of lower recurrence rate and lower retreatment rate in patients who were continued on statin treatment in the postoperative period. It is understandable that the role of statins is more apparent in ruptured aneurysms when inflammatory markers and metalloproteinase expression are increased, and therefore the clinical study by Brinjikji et al.[10] focused on ruptured aneurysms. Conversely, our subgroup analysis showed a significant reduction in recurrence in patients with unruptured aneurysms, whereas the reduction was not significant in ruptured aneurysms. This finding suggests that the beneficial effect of statins is not limited to ruptured aneurysms and raises a possibility that its pathomechanism extends beyond the inflammatory cascade. In the original HEAT study, a lower recurrence was observed with the use of hydrocoils compared with BPCs, which was thought to be due to improved packing density in combination with a better healing mechanism with hydrocoils.[5] In our post hoc matched analysis, both the use of statins and the use of hydrocoils were independently associated with lower recurrence rates; furthermore, the subgroup analysis showed a significant reduction in recurrence with the use of statins and hydrocoils compared with the use of statins with BPCs. This finding highlights the possibility that there could be synergistic effects. It would be interesting to see if the incorporation of statin nanoparticles in the design of coils could accelerate the healing process and thereby reduce recurrence. One animal study using simvastatin-coated coils in rodents demonstrated promising results in this regard, showing accelerated tissue organization with collagen connective matrix in the aneurysm sac as well as at the orifice.[19] Unfortunately, further attempts to develop statin-coated coils and clinical studies are still lacking.

One of the major limitations of this post hoc analysis is that the original HEAT study was not geared toward balancing the factors critical for this analysis; therefore, an indirect method using propensity score matching was utilized to achieve a balanced cohort. Nonetheless, we could not perfectly match the patients in both groups based on aspirin use (and to age) because of the inherent skewed cohort data, despite attempting multiple robust matching protocols. However, the propensity score matching did significantly reduce the selection bias from 41.1% to –2.9%, suggesting a well-balanced cohort (defined as < 5% bias). Aspirin use has been shown to affect aneurysm rupture[20] as well as recanalization after endovascular coiling[21] and therefore merits special consideration with regard to its confounding effect in this analysis, especially with the increased concomitant use of aspirin and statins in the general population. However, in our cohort about one-half of the patients who were taking aspirin were not receiving statin therapy, and about one-third of the patients who were receiving statin therapy were not taking aspirin. Additionally, the univariate logistic regression did not show a significant association of aspirin use with recurrence (OR 0.9, $p = 0.776$). Nevertheless, there is insufficient evidence to eliminate the confounding effect of aspirin use on recurrence rate. Second, although our study found a significant association between statin use and reduced recurrence rate, a direct causal effect cannot be inferred. Third, we did not perform analyses based on the type of statin used to see if a particular class of statins had a more beneficial effect. Finally, the confounding effect of hydrocoils on aneurysm recurrence cannot be ruled out despite the fact that statin therapy and hydrocoil use were found to have independent and significant associations with aneurysm recurrence based on the multivariate analysis.

The healing process of the aneurysm sac after embolization involves multiple physiological mechanisms. We speculate that the interaction of statins in this pathway is complex, and therefore it is likely difficult to predict if a subgroup of patients will benefit from statins. Additionally, the role of statins in preventing recurrence or promoting occlusion is unclear in relation to other embolization methods, including flow diversion, as several studies have failed to show any better clinical or angiographic outcome with the use of statins in patients undergoing treatment with a Pipeline embolization device (Medtronic).[22–25] More studies on intrasaccular devices may help in understanding whether the beneficial effects of statins are due to intrasaccular remodeling/tissue organization or improved endothelialization of the parent vessel.

Conclusions

Our results showed a reduced rate of recurrence with the use of statins in patients undergoing endovascular coiling for IAs, with a decreased need for retreatment in the follow-up period. Subgroup analysis showed that the benefit of statins was significant in patients with unruptured aneurysms and those who underwent coiling with hydrocoils. Considering the relatively low-risk profile of the statins that have been widely used in the cardiovascular world, we envision that statins can be adapted as an effective therapeutic agent to reduce the recanalization of coiled aneurysms. Additional studies are warranted to validate our findings and to better understand the effect of statins on aneurysm healing.

Acknowledgments

The HEAT study was an investigator-initiated trial funded by MicroVention through a grant that was housed at Northwestern University and Mayo Clinic. This study was independently managed by the senior author (B.R.B.). No funding was received for this post hoc analysis.

References

1. Ferns SP, Sprengers MES, van Rooij WJ, et al. Coiling of intracranial aneurysms: a systematic review on initial occlusion and reopening and retreatment rates. *Stroke*. 2009;40(8):e523-e529.

2. Pierot L, Wakhloo AK. Endovascular treatment of intracranial aneurysms: current status. *Stroke*. 2013;44(7):2046-2054.
3. Ogilvy CS, Chua MH, Fusco MR, et al. Validation of a system to predict recanalization after endovascular treatment of intracranial aneurysms. *Neurosurgery*. 2015;77(2):168-174.
4. Ogilvy CS, Chua MH, Fusco MR, Reddy AS, Thomas AJ. Stratification of recanalization for patients with endovascular treatment of intracranial aneurysms. *Neurosurgery*. 2015; 76(4):390-395.
5. Bendok BR, Abi-Aad KR, Ward JD, et al. The Hydrogel Endovascular Aneurysm Treatment Trial (HEAT): a randomized controlled trial of the second-generation hydrogel coil. *Neurosurgery*. 2020;86(5):615-624.
6. Erbs S, Beck EB, Linke A, et al. High-dose rosuvastatin in chronic heart failure promotes vasculogenesis, corrects endothelial function, and improves cardiac remodeling—results from a randomized, double-blind, and placebo-controlled study. *Int J Cardiol*. 2011;146(1):56-63.
7. Liu P, An Q, Chen X, Huang J, Yang GY, Zhu W. Rosuvastatin for enhancement of aneurysm neck endothelialization after coil embolization: promotion of endothelial progenitor cells in a rodent model. *J Neurosurg*. 2016;124(5):1265-1274.
8. Van Kuijk JP, Flu WJ, Witteveen OP, Voute M, Bax JJ, Poldermans D. The influence of statins on the expansion rate and rupture risk of abdominal aortic aneurysms. *J Cardiovasc Surg (Torino)*. 2009;50(5):599-609.
9. Gray C, Goodman P, O'Malley MK, O'Donohoe MK, McDonnell CO. Statins promote residual aneurysm sac regression following endovascular aortic aneurysm repair. *Vasc Endovascular Surg*. 2014;48(2):111-115.
10. Brinjikji W, Shahi V, Cloft HJ, Lanzino G, Kallmes DF, Kadirvel R. Could statin use be associated with reduced recurrence rates following coiling in ruptured intracranial aneurysms? *AJNR Am J Neuroradiol*. 2015;36(11):2104-2107.
11. Chalouhi N, Ali MS, Jabbour PM, et al. Biology of intracranial aneurysms: role of inflammation. *J Cereb Blood Flow Metab*. 2012;32(9):1659-1676.
12. Ferretti G, Bacchetti T, Banach M, Simental-Mendía LE, Sahebkar A. Impact of statin therapy on plasma MMP-3, MMP-9, and TIMP-1 concentrations: a systematic review and meta-analysis of randomized placebo-controlled trials. *Angiology*. 2017;68(10):850-862.
13. Heeba G, Moselhy ME, Hassan M, Khalifa M, Gryglewski R, Malinski T. Anti-atherogenic effect of statins: role of nitric oxide, peroxynitrite and haem oxygenase-1. *Br J Pharmacol*. 2009;156(8):1256-1266.
14. Sawyer DM, Pace LA, Pascale CL, et al. Lymphocytes influence intracranial aneurysm formation and rupture: role of extracellular matrix remodeling and phenotypic modulation of vascular smooth muscle cells. *J Neuroinflammation*. 2016; 13(1):185.
15. Yoshimura Y, Murakami Y, Saitoh M, et al. Statin use and risk of cerebral aneurysm rupture: a hospital-based case-control study in Japan. *J Stroke Cerebrovasc Dis*. 2014;23(2): 343-348.
16. Bekelis K, Smith J, Zhou W, et al. Statins and subarachnoid hemorrhage in Medicare patients with unruptured cerebral aneurysms. *Int J Stroke*. 2015;10(Suppl A100):38-45.
17. Song TJ, Oh SH, Kim J. The impact of statin therapy after surgical or endovascular treatment of cerebral aneurysms. *J Neurosurg*. 2019;133(1):182-189.
18. Brinjikji W, Yong Hong D, Dai D, Schroeder DJ, Kallmes DF, Kadirvel R. Statins are not associated with short-term improved aneurysm healing in a rabbit model of unruptured aneurysms. *J Neurointerv Surg*. 2017;9(2):200-203.
19. Kodama T, Iwata H. Comparison of bare metal and statin-coated coils on rates of intra-aneurysmal tissue organization in a rat model of aneurysm. *J Biomed Mater Res B Appl Biomater*. 2013;101(4):656-662.
20. Abi-Aad KR, Rahme RJ, Syal A, et al. Predictive model evaluating risk of hemorrhage in intracranial aneurysms: analysis from prospectively collected HEAT trial database. *World Neurosurg*. 2023;178:e315-e322.
21. Musmar B, Spellicy SE, Abdelgadir J, Kraljic S, Zomorodi A, Hasan DM. The impact of regular aspirin use on aneurysm recanalization rates after endovascular coiling. *J Neurosurg*. 2024;141(4):1020-1025.
22. Wang X, Turhon M, Yang X, et al. Could statin improve outcomes after pipeline embolization for intracranial aneurysms in a real-world setting? *Ther Adv Neurol Disord*. 2023;16: 17562864231170517.
23. Salih M, Young M, Filo J, Shutran M, Taussky P, Ogilvy CS. Effect of statin on radiographic and clinical outcomes of intracranial aneurysms treated with pipeline embolization: a propensity score-matched analysis. *Neurosurgery*. 2023; 93(5):1000-1006.
24. Brinjikji W, Cloft H, Cekirge S, et al. Lack of association between statin use and angiographic and clinical outcomes after Pipeline embolization for intracranial aneurysms. *AJNR Am J Neuroradiol*. 2017;38(4):753-758.
25. Salem MM, Maragkos GA, Enriquez-Marulanda A, et al. Statin therapy and diabetes do not affect aneurysm occlusion or clinical outcomes after Pipeline Embolization Device treatment: a preliminary study. *World Neurosurg*. 2018;120: e525-e532.
26. Roy D, Milot G, Raymond J. Endovascular treatment of unruptured aneurysms. *Stroke*. 2001;32(9):1998-2004.

Disclosures

Dr. Levy reported shareholder/ownership in NeXtGen Biologics, Rapid Medical, Claret Medical, Cognition Medical, Imperative Care (formerly the Stroke Project), StimMed, Three Rivers Medical, Q'Apel, and Dendrite; national PI for Penumbra THUNDER, Medtronic SHIELD, and Medtronic (formerly Covidien Neurovascular) steering committees for SWIFT Prime and SWIFT Direct Trials; site PI for MicroVention CONFIDENCE Study and Medtronic (formerly Covidien Neurovascular) STRATIS Study–Sub I; honorarium for training and lectures from Medtronic (formerly Covidien Neurovascular), Penumbra, MicroVention, and Integra; consulting fees from Clarion, GLG Consulting, Guidepoint Global, Medtronic (formerly Covidien Neurovascular), StimMed, and Mosaic; chief medical officer for Haniva Technology; advisory board for NeXtGen Biologics, Cognition Medical, Endostream Medical, and IRRAS AB; leadership or fiduciary role (board, society, committee, or advocacy groups—paid or unpaid) for Congress of Neurological Surgeons, American Board of Neurological Surgery, and University at Buffalo Neurosurgery outside the submitted work. In addition, Dr. Levy had a patent for Ultrasonic Surgical Blade pending and is an expert witness for Medical Legal Review. Dr. Siddiqui reported grants from NIH (co-investigator, 1R01EB030092-01), Brain Aneurysm Foundation Carol W. Harvey Chair of Research (mentor), and Sharon Epperson Chair of Research; stock/stock options in Adona Medical, Basecamp Vascular SAS, Bend IT Technologies, BlinkTBI, Borvo Medical, Cerebrotech Medical Systems, CerebrovaKP, Code Zero Medical, Cognition Medical, Collavidence, Contego Medical, CVAID, E8, Endostream Medical, FreeOx Biotech, Galaxy Therapeutics, Hyperion Surgical, Imperative Care, InspireMD, Instylla, Launch NY, Neurolutions, NeuroRadial Technologies (sold to Medtronic in 2021), Neurovascular Diagnostics, Peijia Medical, PerFlow Medical, Piraeus Medical, Q'Apel Medical, QAS.ai, Radical Catheter Technologies, Rebound Therapeutics (purchased by Integra LifeSciences in 2019), Rist Neurovascular (purchased by Medtronic in 2020), Sense Diagnostics, Serenity Medical, Silk Road Medical, Sim & Cure, Spinnaker Medical, StimMed, Synchron, Tulavi Therapeutics, Vastrax, Viseon, Whisper

Medical, and Willow Medtech; consulting fees from Amnis Therapeutics, Asahi Intecc, Boston Scientific, Canon Medical Systems USA, Cardinal Health 200, Cerebrotech Medical Systems, CerebrovaKP, Cerenovus, Contego Medical, Cordis, Corindus, Endostream Medical, FreeOx Biotech, Hyperfine Operations, Imperative Care, InspireMD, Integra, IRRAS, Medtronic, MicroVention, Minnetronix Neuro, Peijia Medical, Penumbra, Piraeus Medical, Q'Apel Medical, Rapid Medical, Serenity Medical, Shockwave Medical, Silk Road Medical, StimMed, Stryker Neurovascular, Synchron Australia, VasSol, Vesalio, Viz.ai, and WL Gore; and national PI/steering committees of Cerenovus EXCELLENT and ARISE II Trial; Medtronic SWIFT PRIME, VANTAGE, EMBOLISE, and SWIFT DIRECT Trials; MicroVention FRED Trial and CONFIDENCE Study; MUSC POSITIVE Trial; Penumbra 3D Separator Trial, COMPASS Trial, INVEST Trial, and MIVI Neuroscience EVAQ Trial; Rapid Medical SUCCESS Trial; and InspireMD C-GUARDIANS outside the submitted work. In addition, Dr. Siddiqui had a patent for Patent No. US 11,464,528 B2 (October 11, 2022).

Author Contributions

Conception and design: Bendok, Patra, Abi-Aad, Siddiqui, Veznedaroglu. Acquisition of data: Patra, Abi-Aad, Ogilvy, Levy, Siddiqui. Analysis and interpretation of data: Patra, Ogilvy, Levy, Batjer. Drafting the article: Patra, Abi-Aad, Ogilvy. Critically revising the article: Bendok, Patra, Turcotte, Levy, Veznedaroglu, Batjer. Reviewed submitted version of manuscript: Patra, Abi-Aad, Turcotte, Levy, Siddiqui, Batjer. Approved the final version of the manuscript on behalf of all authors: Bendok. Statistical analysis: Patra, Abi-Aad. Administrative/technical/material support: Turcotte, Ogilvy, Siddiqui. Study supervision: Bendok, Ogilvy, Levy, Siddiqui.

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