Submacular Hemorrhage Rates Following Anti-Vascular Endothelial Growth Factor Injections for Exudative Age-Related Macular Degeneration

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• PURPOSE: To examine rates of submacular hemorrhage in patients undergoing anti-vascular endothelial growth factor (VEGF) injections, comparing rates between specific anti-VEGF agents.

• DESIGN: Retrospective clinical cohort study.

• METHODS: All patients in the database from January 2015 to November 2023 with a diagnosis of neovascular age-related macular degeneration and accompanying submacular hemorrhage (SMH). SMH prevalence and associated anti-VEGF injection type were analyzed in 140,915 eyes (of which 9107 had SMH) in a nationwide aggregated electronic health care database using chi-square test of proportion. Visual acuity (VA) data was assessed using 2-sample independent t-tests. The primary outcome was rate of SMH per injection type. Secondary datapoints examined were time between SMH diagnosis and last anti-VEGF injection, number of injections before SMH, treatment interval at time of SMH, VA before and at 12 months after SMH, eyes undergoing pars plana vitrectomy (PPV) within 30 days of SMH, and VA before PPV and at 12 months after PPV.

• RESULTS: The last injection type in eyes with SMH was bevacizumab in 3430 (37.8%) eyes, brolucizumab-dbll in 46 (0.51%) eyes, aflibercept in 3221 (35.4%) eyes. Ranibizumab in 2246 (24.7%) eyes, and faricimab-svoa in 155 (1.7%) eyes. Rates of SMH were significantly higher ($P \leq .001$) for last injection with bevacizumab compared to every other injection type. Rates of SMH were significantly lower ($P = .0004$) for last injection with faricimab-svoa or ranibizumab injections each had significantly shorter (mean and standard deviation 48.9 (27.9), $P < .02$; mean and standard deviation 59.6 (38.2), $P = .003$, respectively) mean time between SMH diagnosis and last injection than did patients undergoing any other injection. Mean VA before SMH and at 12 months after SMH did not significantly differ by injection type among all patients. The number of patients who underwent PPV were 52 (1.51%) for bevacizumab, 4 (8.7%) for brolucizumab-dbll, 58 (1.8%) for aflibercept, 41 (1.8%) for ranibizumab, and 3 (1.9%) for faricimab-svoa. Mean VA before SMH and at 12 months after SMH did not significantly differ by injection type in patients undergoing PPV.

• CONCLUSIONS: Faricimab may be more protective than other anti-VEGF injections against SMH in patients with neovascular age-related macular degeneration. (Am J Ophthalmol 2025;270: 172–182. © 2024 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.)

INTRODUCTION

Submacular hemorrhage (SMH) is a potential complication of neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy, and it can often lead to severe vision loss.[1-7] Risk factors leading to SMH have yet to be well-defined, but SMH has been observed in patients on anticoagulant therapy, antiplatelet therapy, and in patients with coagulopathy.[8] One study specifically looking at risk factors for SMH found that choroidal neovascularization with disciform scars specifically increased risk of SMH, while age and presenting visual acuity (VA) were not associated with SMH onset.[7] Use of anti-vascular endothelial growth factor (VEGF) agents has been shown to reduce the risk of SMH in patients with nAMD.[9] The treatment of SMH also varies, from continued anti-VEGF injections to pars plana vitrectomy (PPV) with subretinal tissue plasminogen activator and/or pneumatic displacement, as well as in-office pneumatic displacement.[10,11] Recently, there has been work to show similar efficacy of multiple subretinal anti-VEGF agents in the treatment of SMH,[12] and a randomized controlled trial of 90 patients found no significant difference in PPV vs pneumatic displacement for treat-

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ment of SMH in patients with nAMD with intravitreal anti-VEGF added to each arm.[11] Thus, the best evidence-directed treatment of SMH due to nAMD continues to evolve but has included both surgery and intravitreal injections.

As SMH can quickly become sight-threatening, previous studies have attempted to define optimal treatment regimens for nAMD that both treat underlying disease and do not increase risk of SMH. It has been found that individualized treat-and-extend treatment regimens with ranibizumab are noninferior to fixed-dose regimens for the treatment of nAMD,[13-17] but relatively little research has examined subsequent incidence and treatment of SMH specifically, and the effects of these regimens on SMH. A retrospective analysis of 7642 eyes found that more injections may increase total overall risk, but each successive injection did not significantly increase probability of SMH.[7] One retrospective cohort study of 42 eyes found that the timing of large SMH requiring PPV with subretinal tissue plasminogen activator was not associated with prolonged dosing intervals or recent interval extension in patients undergoing treat-and-extend regimens for nAMD.[6] However, SMH is known to occur even after stabilization, so more studies into the factors surrounding new SMH of any size are needed.[18]

Furthermore, it remains unknown whether specific anti-VEGF treatments are associated with differing risks of SMH; some work has suggested that there is no significant difference in SMH risk between bevacizumab and either aflibercept or ranizumab.[7] While there exists some evidence that treat-and-extend regimens using bevacizumab, ranibizumab, and aflibercept are not associated with increased large SMH, more work remains to determine the rates of SMH in patients receiving anti-VEGF injections, especially given that SMH is sometimes treated without PPV. Thus, we examined the rates of SMH with and without surgical treatment in patients undergoing anti-VEGF injections, comparing rates between specific anti-VEGF agents and examining treatment intervals using a large, real-world healthcare database.

METHODS

We performed a retrospective cohort study of patients from a nationwide aggregated electronic health care database (Vestrum Health, LLC) comprising 74 private practice retinal centers in the United States encompassing approximately 2.6 million unique patients and 19.9 million encounters as of January 2024.

This study analyzed all eyes diagnosed with nAMD and accompanying SMH within the Vestrum database from January 2015 to November 2023. Patients were excluded if they were not new to the database (ie, treated elsewhere before index date), had no valid gender recorded, did not receive anti-VEGF treatment, or if they were previously diagnosed with SMH. Patients were identified using the diagnosis-related free texts "submacular hemorrhage, subretinal hemorrhage, submacular heme, submacular sub-RPE, SRH, and SMH." Injection type was determined using the last anti-VEGF visit prior to SMH diagnosis and included bevacizumab (Avastin, Genentech/Roche, Inc.), brolucizumab-dbll (Beovu, Novartis Pharmaceuticals), aflibercept (Eylea, Regeneron Pharmaceuticals, Inc.), ranibizumab (Lucentis, Genentech/Roche, Inc.), and faricimab-svoa (Vabysmo, Genentech/Roche, Inc.). The primary outcome was rate of SMH per injection type within the cohort with secondary analyses examining time between SMH diagnosis and last anti-VEGF injection, total number of injections before SMH, treatment interval at time of SMH, VA before and at 12 months after SMH, eyes undergoing PPV within 30 days of SMH, and VA before PPV and at 12 months after PPV. Patient historical factors obtained included anticoagulation or antiplatelet use and presence of wet or dry AMD in the fellow eye.

For statistical analysis, we used R Statistical Software (v4.1.3; R Core Team), and Microsoft Excel (Microsoft Corporation) was used for data storage. For analysis of SMH prevalence and associated anti-VEGF injection type, chi-square test of proportion was used and a 2-sample independent *t* test was used for VA data. Mann–Whitney *U* test was used to compare median days from nAMD diagnosis/first anti-VEGF injection/first injection with current anti-VEGF agent to SMH by anti-VEGF injection type. A *P* value less than .05 was considered to be statistically significant. For analysis of odds of SMH, a multivariate logistic regression was performed with SMH occurrence as the dependent variable assessing age, gender, antiplatelet use, anticoagulant use, type of anti-VEGF agent (either last agent before SMH or last agent at final follow-up if no SMH), and mean total number of injections (before SMH or at final follow-up) on SMH risk.

RESULTS

A total of 254,505 eyes diagnosed with nAMD were identified during the study period, of which 140,915 met the inclusion criteria. Of the patients included in the study, 52,445 (37%) were male and 88,470 (63%) were female with a mean age of 79 and standard deviation (SD) of 8.9 years (Table 1). Among the 140,915 eyes diagnosed with nAMD and receiving anti-VEGF injections, there were 1938,305 total injections, of which 546,817 (28.2%) were bevacizumab, 12,067 (0.62%) were brolucizumab-dbII, 787,172 (40.6%) were aflibercept, 519,244 (26.8%) were ranibizumab, 72,930 (3.8%) were faricimab-svoa, and 75 (0.0039%) were ranibizumab implant (Susvimo, Genentech/Roche, Inc., not included in study analysis due to limited data). A total of 9107 (6.46%) eyes within the cohort were diagnosed with SMH following initiation of anti-

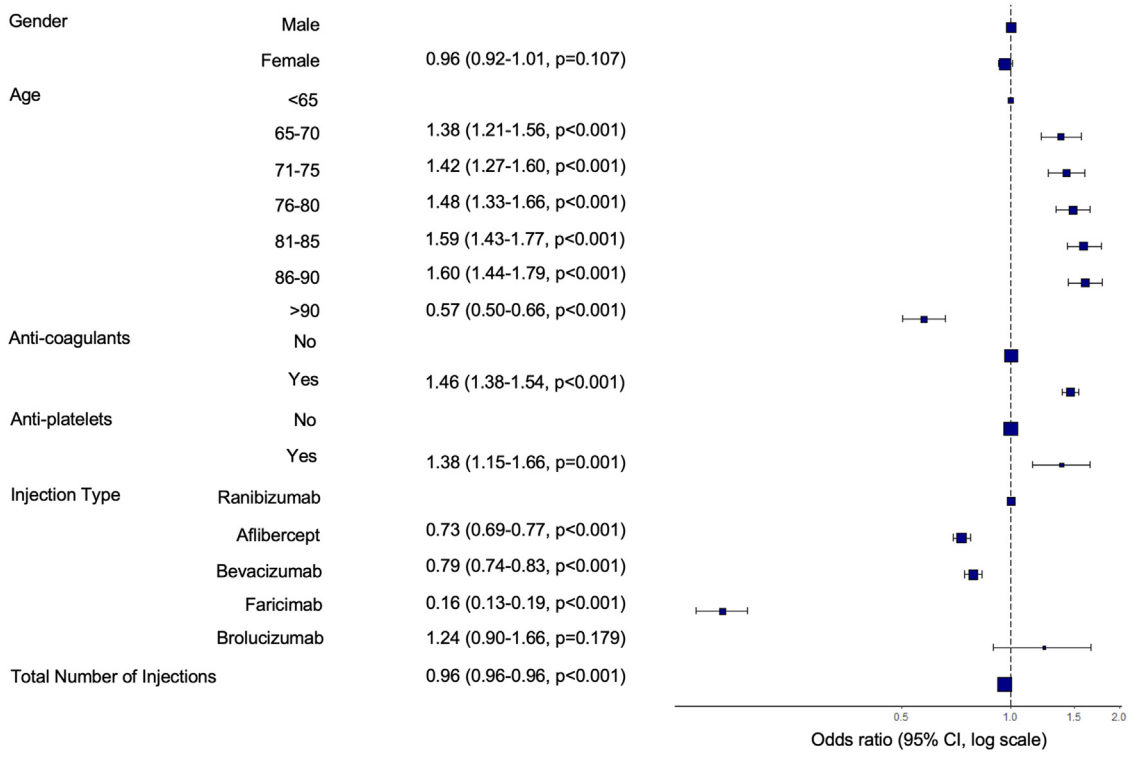

FIGURE 1. Logistic regression displaying odds of submacular hemorrhage by gender, age, and medication use. CI = confidence interval.

TABLE 1. Demographics of All Eyes

Demographics	All Eyes
Number of eyes	140,915
Mean age (SD)	79 (8.9)
Male %	3514 (39%)
Female %	5593 (61%)
Number of injections	
bevacizumab (Avastin)	546,817
brolucizumab-dbll (Beovu)	12,067
aflibercept (Eylea)	787,172
ranibizumab (Lucentis)	519,244
faricimab-svoa (Vabysmo)	72,930

SD = standard deviation.

VEGF therapy for exudative AMD. Multivariate logistic regression found significantly increased odds of SMH in patients who were age 65 to 90, on an anticoagulant, and on an antiplatelet agent, and there were significantly decreased odds of SMH in patients who were older than 90 years old as well as the use of aflibercept, faricimab, bevacizumab (compared to ranibizumab as the index metric) and higher total number of injections (Figure 1).

Of the eyes diagnosed with SMH, the last injection type was bevacizumab in 3439 (37.8%) eyes, brolucizumab-dbII in 46 (0.51%) eyes, aflibercept in 3221 (35.4%) eyes, ranibizumab in 2246 (24.7%) eyes, and faricimab-svoa in 155 (1.7%) eyes (Table 2). Rates of SMH were significantly higher ($P \leq .001$) for last injection with bevacizumab compared to every other injection type. Rates of SMH were significantly lower ($P = .0004$) for last injection with faricimab-svoa compared to every other injection type (Figure 2). The mean time between SMH diagnosis and the last anti-VEGF injection administered was 61.1 days (SD 38.9) with a median time interval of 48 days. The mean time between SMH diagnosis and last injection was 61.0 days (SD 39.8) for bevacizumab patients, 61.4 days (SD 30.7) for brolucizumab-dbII patients, 62.8 (SD 38.7) for aflibercept patients, 59.6 (SD 38.2) for ranibizumab patients, and 48.9 (SD 27.9) for faricimab-svoa patients (Figure 3). Patients receiving faricimab-svoa injections had significantly shorter ($P < .02$) mean time between SMH diagnosis and last injection than did patients undergoing any other injection. Patients receiving ranibizumab injections had significantly shorter ($P = .003$) mean time between SMH diagnosis and last injection than did patients undergoing aflibercept injections. The mean treatment interval at time of SMH was 68.4 days for all patients, 71.4 for bevacizumab patients, 61.1 for brolucizumab-dbII patients, 69.9 for aflibercept patients, 63.3 for ranibizumab patients, and 50.8 for faricimab-svoa patients. The mean number of injections prior to SMH was 8.4 in all patients

TABLE 2. Demographics of Eyes With Submacular Hemorrhage

	All Eyes	Bevacizumab	Brolucizumab-dbll	Aflibercept	Ranibizumab	Faricimab-svoa
Number of eyes with SMH	9107	3439	46	3221	2246	155
Mean age (SD)	79.5 (8.0)	80 (8.2)	76 (7.8)	79 (8.0)	80 (7.7)	79 (7.8)
Male %	3514 (39%)	1218 (37%)*	21 (46%)	1337 (41%)*	809 (36%)	66 (43%)
Female %	5593 (61%)	2157 (63%)*	25 (54%)	1886 (59%)*	1436 (64%)	89 (57%)
Number of eyes with anticoagulation use (%)	1467 (16%)	537 (16%)	10 (22%)	545 (17%)	350 (16%)	25 (16%)
Number of eyes with antiplatelet use (%)	85 (1%)	34 (1%)	1 (2%)	26 (1%)	22 (1%)	2 (1%)
Dry AMD in fellow eye	3172 (35%)	1299 (38%)*	16 (35%)	1046 (32%)	754 (34%)	57 (37%)
Wet AMD in fellow eye	5550 (61%)	1955 (58%)*	28 (61%)	2018 (63%)	1414 (63%)	95 (61%)

AMD = age-related macular degeneration; SD = standard deviation; SMH = submacular hemorrhage.

*indicates statistical significance ($P < .05$) vs another injection type. For Male %, bevacizumab was significantly less than aflibercept, and aflibercept was significantly more than ranibizumab. For Female %, bevacizumab was significantly more than aflibercept, and aflibercept was significantly less than ranibizumab. For Dry AMD in fellow eye, bevacizumab was significantly more than both aflibercept and ranibizumab. For Wet AMD in fellow eye, bevacizumab was significantly less than both aflibercept and ranibizumab. All other between-group comparisons did not reach statistical significance.

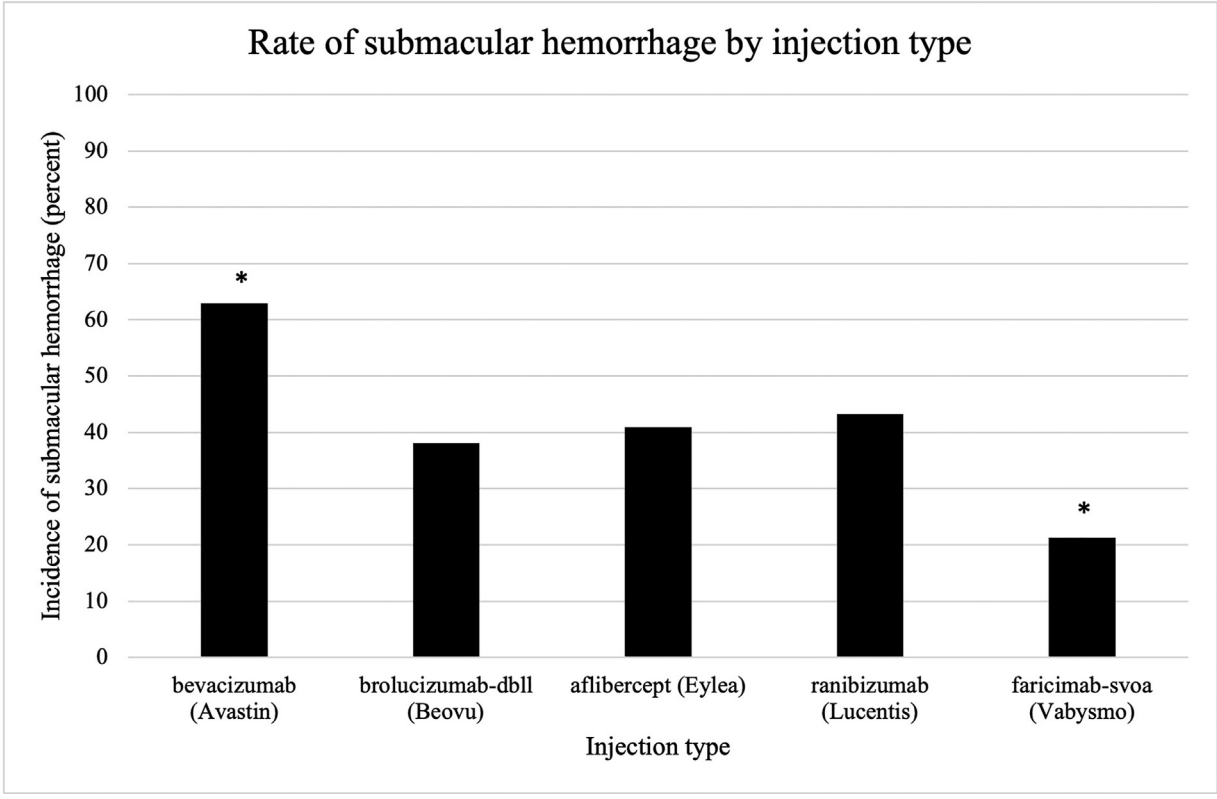

FIGURE 2. Submacular hemorrhage by last injection type. "*" indicates significant difference ($P \leq .001$) compared to every other injection type.

with SMH. The mean number of injections prior to SMH was 5.1 for bevacizumab, 18.1 for brolucizumab-dbII, 10.8 for aflibercept, 9.3 for ranibizumab, and 14.8 for faricimab-svoa. Many injections were performed after switching from a different agent. Table 3 displays, for each injection prior to SMH, which agents had been used prior to the current agent. Percentages sometimes exceed 100%, as some patients switched through multiple agents, and may not always add up to 100%, as some patients did not switch agents.

Duration of treatment in days from diagnosis of nAMD to SMH, from first anti-VEGF injection of any type to SMH, and from first injection with the patient's current anti-VEGF agent to SMH are provided in Table 4. Me-

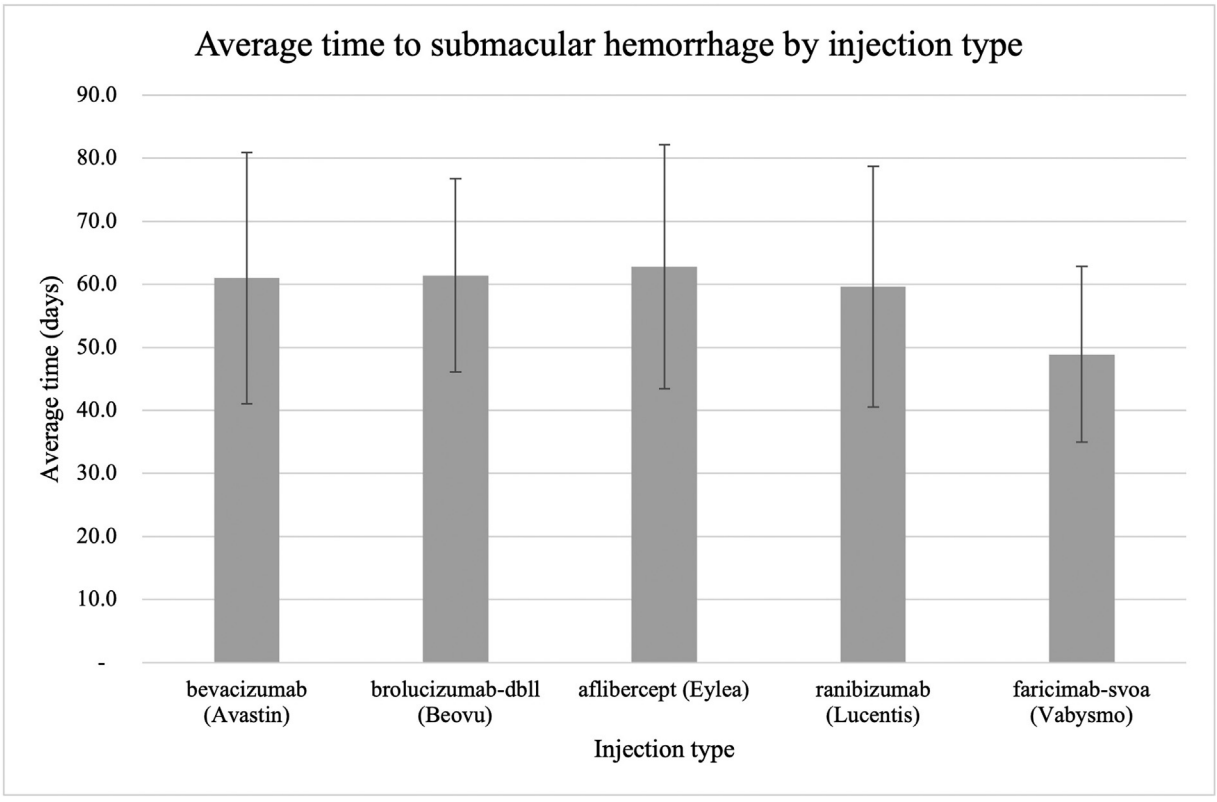

FIGURE 3. Average time in days from submacular hemorrhage to last injection by injection type. Bars show standard deviation. Faricimab-svoa had a statistically significant shorter average time from last injection to SMH than all other injection types ($P < .02$). Ranibizumab had a statistically significant shorter average time from last injection to SMH than aflibercept ($P = .003$).

TABLE 3. Data On Switching Agents

Injection Type Used Prior to Current Agent	Bevacizumab	Brolucizumab-dbll	Aflibercept	Ranibizumab	Faricimab-svoa
Bevacizumab		22 (48%)	997 (31%)	417 (19%)	64 (41%)
Brolucizumab-dbll	11 (0%)		39 (1%)	8 (0%)	11 (7%)
Aflibercept	124 (4%)	35 (76%)		174 (8%)	79 (51%)
Ranibizumab	105 (3%)	15 (33%)	450 (14%)		36 (23%)
Faricimab-svoa	4 (0%)	1 (2%)	8 (0%)	0 (0%)	

The first column displays injection types used prior to switching to the agent being used at the time of submacular hemorrhage (first row); number and percentages shown are total out of all injections of that type that were given prior to a submacular hemorrhage. Percentages do not add up to 100% and may exceed 100%, as not all patients switched agents, and some patients switched between multiple agents prior to submacular hemorrhage.

dian days from nAMD diagnosis to SMH were 280 for bevacizumab, 455 for brolucizumab-dbll, 366 for aflibercept, 388 for ranibizumab, and 70 for faricimab-svoa ($P < .0001$ bevacizumab vs aflibercept, ranibizumab, and faricimab-svoa; $P < .0001$ faricimab-svoa vs all other medications). Median days from first anti-VEGF injection of any type to SMH were 259 for bevacizumab, 315 for brolucizumab-dbll, 329 for aflibercept, 351 for ranibizumab, and 62 for faricimab-svoa ($P < .0001$ bevacizumab vs aflibercept, ranibizumab, and faricimab-svoa; $P < .0001$ faricimab-svoa vs all other medications). Median days from first anti-VEGF injection of the patient's currently used anti-VEGF agent to SMH were 175 for bevacizumab, 238 for brolucizumab-dbll, 322 for aflibercept, 294 for ranibizumab, and 113 for faricimab-svoa ($P < .0001$ bevacizumab vs aflibercept, ranibizumab, and faricimab-svoa; $P < .0001$ faricimab-svoa vs all other medications).

A total of 9044 eyes (99%) had VA recorded before SMH. Mean VA (ETDRS letters) before SMH and at 12 months after SMH was 48.5 (SD 26.8) and 48.5 (SD 27.9) for all eyes, 48.7 (SD 26.5) and 48.7 (SD 27.8) for bevacizumab, 50.6 (SD 26.8) and 48.6 (SD 28.8) for

TABLE 4. Time in Days Until SMH From (a) nAMD Diagnosis, (b) First Anti-VEGF Injection of Any Type, and (c) First Injection of Current Medication

a.

	Bevacizumab	Brolucizumab-dbll	Aflibercept	Ranibizumab	Faricimab-svoa
Number of eyes	4665	13	2191	2196	42
Mean days (SD)	494 (538.4)	593 (450.9)	578 (601.9)	601 (606.9)	120 (137.4)
Median days	280[a]	455	366	388	70[b]

b.

	Bevacizumab	Brolucizumab-dbll	Aflibercept	Ranibizumab	Faricimab-svoa
Number of eyes	4665	13	2191	2196	42
Mean days (SD)	474 (528.8)	578 (458.4)	547 (591.0)	576 (598.8)	89 (74.9)
Median days	259[a]	315	329	351	62[b]

c.

	Bevacizumab	Brolucizumab-dbll	Aflibercept	Ranibizumab	Faricimab-svoa
Number of eyes	3439	46	3221	2246	155
Mean days (SD)	354 (439.2)	333 (293.4)	523 (556)	505 (541.1)	152 (125.6)
Median days	175[a]	238	322	294	113[b]

nAMD = neovascular age-related macular degeneration; SD = standard deviation.
[a]$P < .0001$ bevacizumab vs aflibercept, ranibizumab, and faricimab-svoa.
[b]$P < .0001$ faricimab-svoa vs all other medications.

brolucizumab-dbII, 49.1 (SD 26.6) and 48.8 (SD 27.6) for aflibercept, 47.3 (SD 27.4) and 47.7 (SD 28.3) for ranibizumab, and 56.7 (SD 21.0) and 52.8 (SD 27.8) for faricimab-svoa (Figure 4). A total of 9020 eyes (99%) had VA recorded before SMH and at time of SMH. Mean VA (ETDRS letters) before SMH and at time of SMH was 51.5 and 46.1 for all eyes, 50.8 and 46.0 for bevacizumab, 56.0 and 47.0 for brolucizumab-dbll, 53.1 and 46.7 for aflibercept, 50.5 and 45.2 for ranibizumab, and 52.5 and 46.4 for faricimab-svoa (Figure 5). The differences between mean VA by injection type before SMH and at 12 months after SMH were not statistically significant.

A total of 5 eyes (0.05%) with SMH in the dataset underwent pneumatic displacement: 1 bevacizumab, 3 aflibercept, and 1 ranibizumab patient. A total of 158 eyes (1.7%) underwent PPV within 30 days of SMH, and of these, 121 eyes had VA recorded before surgery (77%). The number of patients undergoing PPV and receiving injections were 52 (1.51%) with 39 (75%) having VA for bevacizumab, 4 (8.7%) with 4 (100%) having VA for brolucizumab-dbII, 58 (1.8%) with 42 (72%) having VA for aflibercept, 41 (1.8%) with 33 (80%) having VA for ranibizumab, and 3 (1.9%) with 3 (100%) having VA for faricimab-svoa. There were no significant differences in VA change by injection type at 12 months after SMH. Mean VA before PPV and at 12 months after PPV was 11.1 and 24.7 for all eyes, 12 and 19.4 for bevacizumab, 25 and 64.0 for brolucizumab-dbII, 7 and 23.6 for aflibercept, 12 and 25.4 for ranibizumab, and 65 and 80 for faricimab-svoa (Figure 6). The mean number of days from last injection to PPV was 41.4 (SD 28.1) for all eyes, 37.6 (SD 29.6) for bevacizumab, 37.5 (SD 30.8) for brolucizumab-dbII, 46.1 (SD 31.5) for aflibercept, 39.9 (SD 20.6) for ranibizumab, and 42.0 (SD 20.1) for faricimab-svoa. The mean number of days from SMH to PPV was 6.9 (SD 7.5) for all eyes, 7.6 (SD 7.6) for bevacizumab, 3.5 (SD 7.0) for brolucizumab-dbII, 5.9 (SD 6.0) for aflibercept, 7.3 (SD 8.6) for ranibizumab, and 15.0 (SD 14.5) for faricimab-svoa. Indications for PPV were available for 122 eyes (77%) and included serous retinal detachment (16 eyes, 10%), vitreous hemorrhage (28 eyes, 18%), and retinal hemorrhage (78 eyes, 49%).

There were 8895 total eyes (98%) with SMH that did not undergo PPV and did have VA recorded. Of eyes with VA not undergoing PPV, there were 3362 eyes in the bevacizumab subgroup (99% of bevacizumab eyes) with a mean VA (calculated at time of SMH diagnosis) of 46.6, 41 eyes (91%) in the brolucizumab-dbII subgroup with a mean VA of 46.5, 3141 eyes (98%) in the aflibercept subgroup with a mean VA of 50.4, 2198 eyes (98%) in the ranibizumab subgroup with a mean VA of 53.0, and 153 eyes (99%) in the faricimab-svoa subgroup with a mean VA of 47.6 (Figure 7).

DISCUSSION

This retrospective cohort study of a representative national U.S. database of aggregated electronic medical records

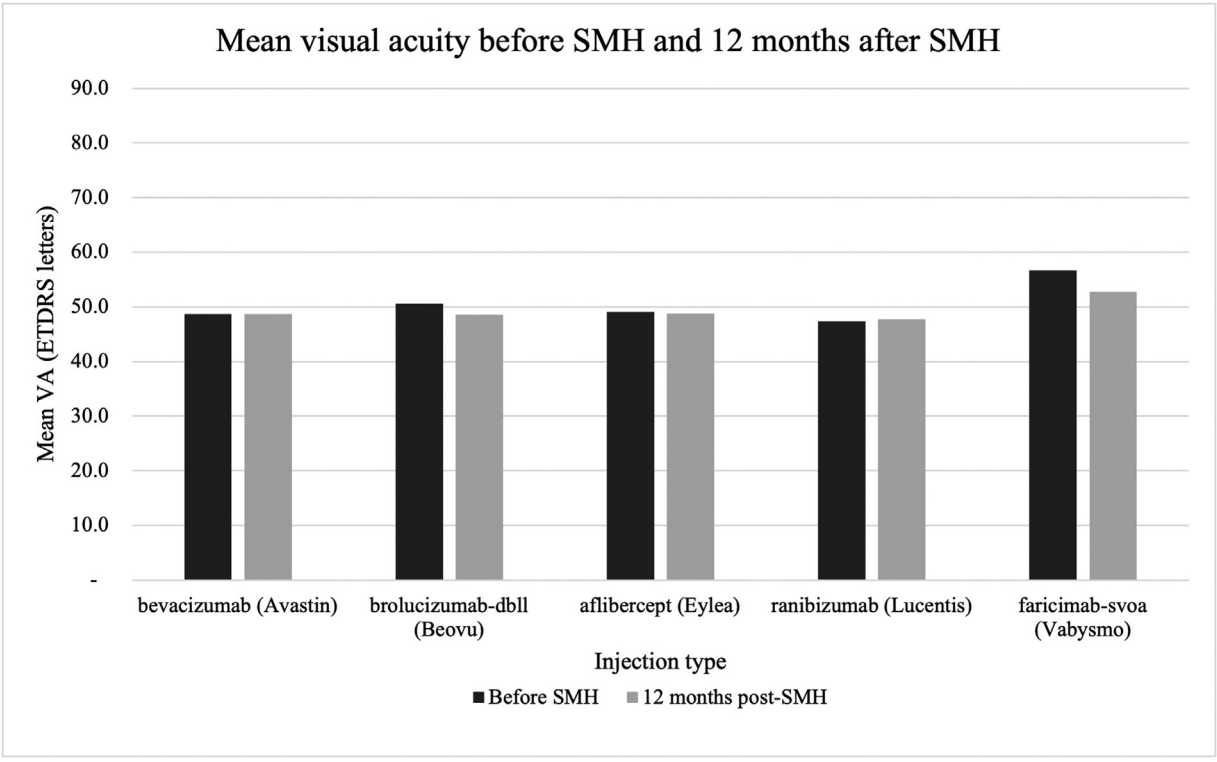

FIGURE 4. Mean visual acuity before and 12 months after submacular hemorrhage by injection type. ETDRS = Early Treatment Diabetic Retinopathy Study; SMH = submacular hemorrhage; VA = visual acuity.

aimed to examine the rates of SMH in patients with age-related macular degeneration receiving anti-VEGF therapy. SMH, while uncommon, can be a devastating complication of neovascular AMD.[7]

Logistic regression of the entire population of eyes ($n = 140{,}915$) with and without SMH found that age 65 to 90 and use of anticoagulants and antiplatelets were associated with increased odds of SMH. Age >90 were associated with lower odds of SMH as was the use of faricimab, aflibercept, and bevacizumab, and higher mean total injections. The reasons why age >90 was associated with lower odds of SMH is unclear; perhaps more elderly patients have more quiescent disease less likely to cause SMH or more prolonged disease and duration of therapy, as it does appear fewer injections may be more prone to SMH as seen in this study. Perhaps unsurprisingly, antiplatelet use and anticoagulant use were both associated with increased odds of SMH. It is interesting that all agents had protective effects against SMH development compared to ranibizumab as a control index, but clearly, faricimab had the highest protective effect, with an odds ratio of 0.16. Taking into account this finding on multivariate analysis and the data on only the eyes that developed SMH (only 1.7% were last treated with faricimab), it is likely that faricimab has a possible protective effect against SMH, more so than other anti-VEGF agents. Even more so when examining the time to SMH based on AMD diagnosis, as eyes treated with bevacizumab and faricimab had a shorter time from diagnosis and last injection to SMH occurrence compared to ranibizumab and aflibercept. Perhaps those eyes treated with faricimab that develop SMH, are more likely to develop SMH regardless of drug as they develop SMH much sooner during the disease course. Alternatively, eyes treated with faricimab may do better in terms of VA and the possible protective effect against SMH in that eyes treated with faricimab were not under treatment as long as the eyes in the other cohorts.

Analyses examining the 9107 total eyes with SMH found that rates of SMH, while low, were significantly higher for last injection with bevacizumab (0.63% of bevacizumab patients) vs brolucizumab-dbII, aflibercept, ranibizumab, and faricimab-svoa. Additionally, rates of SMH were significantly lower for faricimab-svoa patients (0.21%) vs every other injection type. This study uniquely demonstrates the difference in rates of SMH between different intravitreal drugs used to treat neovascular AMD. In this study, the mean time between SMH diagnosis and last anti-VEGF injection was 61.1 days, which is longer than in previous studies primarily looking at SMH requiring surgery; however, in that study, 36% of patients were treatment naïve at time of SMH.[6] Additionally, faricimab-svoa patients in this study had a significantly shorter interval from last injection to SMH (48.9 days) than any other injection type, along with a significantly lower rate of SMH vs other injection types and higher number of overall injections before developing

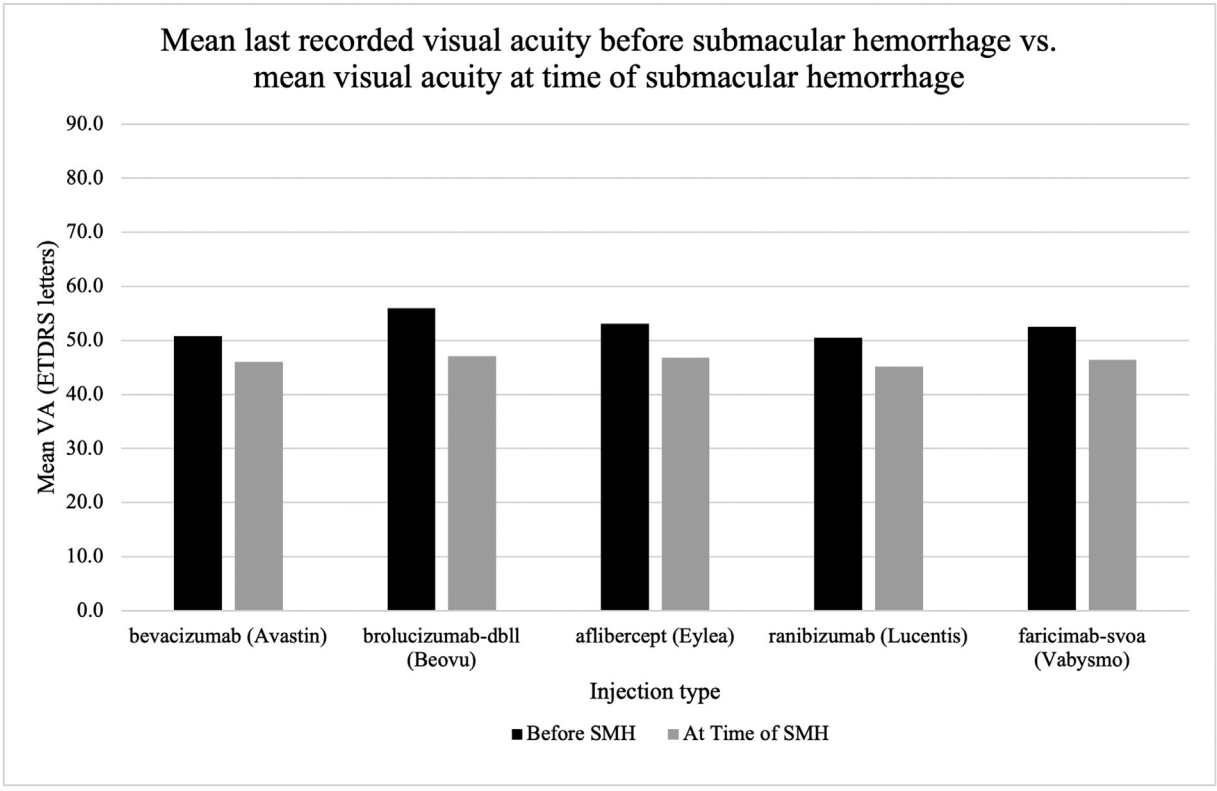

FIGURE 5. Mean last recorded visual acuity before submacular hemorrhage and mean visual acuity at time of SMH. ETDRS = Early Treatment Diabetic Retinopathy Study; SMH = submacular hemorrhage; VA = visual acuity.

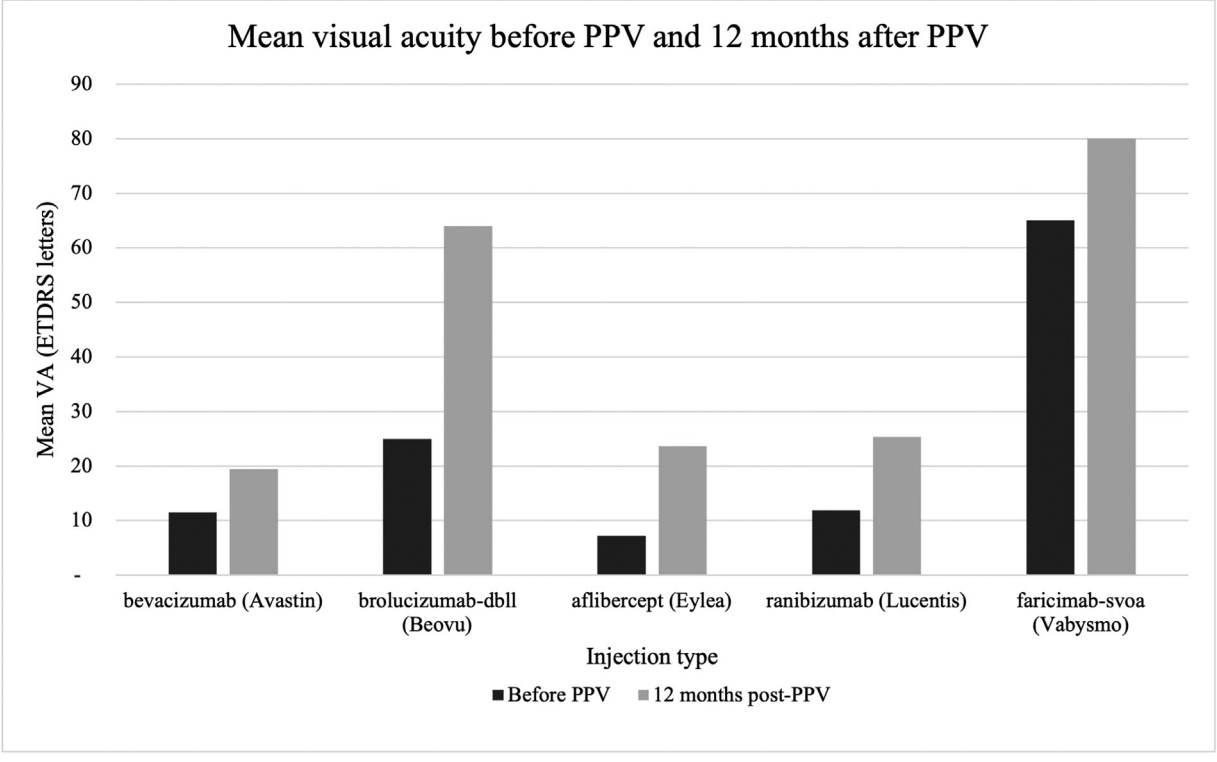

FIGURE 6. Mean visual acuity before and 12 months after pars plana vitrectomy for submacular hemorrhage. ETDRS = Early Treatment Diabetic Retinopathy Study; PPV = pars plana vitrectomy; SMH = submacular hemorrhage; VA = visual acuity.

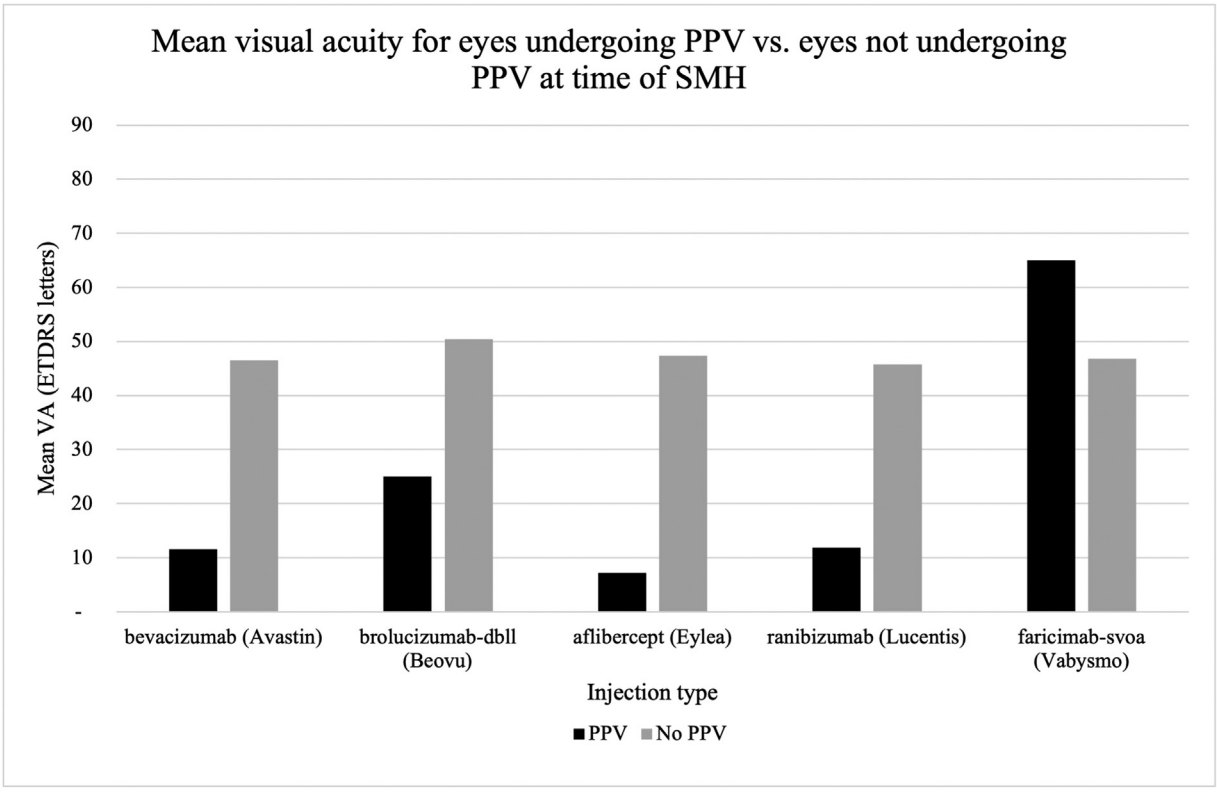

FIGURE 7. Mean visual acuity for eyes undergoing PPV vs eyes not undergoing PPV at time of SMH. ETDRS = Early Treatment Diabetic Retinopathy Study; PPV = pars plana vitrectomy; SMH = submacular hemorrhage; VA = visual acuity.

an SMH. Faricimab-svoa may protect against SMH development, as evidenced by the data presented, but even patients with difficult-to-treat disease (ie, requiring faricimab-svoa use) will still develop SMH, and thus these patients will develop SMH sooner following the last injection despite continued aggressive therapy.

Frequency of switching anti-VEGF agents was also examined, finding that 19% to 48% of patients on a nonbevacizumab agent were previously on bevacizumab. This aligns with common practice patterns of initiating bevacizumab early due to bevacizumab's availability and low cost; additionally, bevacizumab patients tended to have fewer injections than other agents. This complicates the analysis, as patients on bevacizumab may be more likely to have early, uncontrolled disease, without prior exposure to anti-VEGF agents. Thus, bevacizumab may appear to be less protective against SMH than other agents such as faricimab. However, based solely on rates of SMH and controlling for the number of injections in the regression analysis, these data suggest that bevacizumab injections may be slightly less protective of SMH than other faricimab and aflibercept and that faricimab-svoa injections may be slightly more protective against SMH in patients with neovascular AMD. Alternatively, it may be that eyes with poor visual potential may remain on bevacizumab long-term and are less likely to undergo invasive measures if an SMH develops.

The study also examined duration of treatment, comparing time from initial nAMD diagnosis to SMH, time from first anti-VEGF injection of any type to SMH, and time from first anti-VEGF injection of the patient's currently used agent to SMH among each injection type. Bevacizumab was found to have significantly shorter median time until SMH from nAMD diagnosis, first anti-VEGF injection of any type, and first anti-VEGF injection of bevacizumab than aflibercept and ranibizumab. Faricimab was found to have significantly shorter median time until SMH from nAMD diagnosis, first anti-VEGF injection of any type, and first anti-VEGF injection of faricimab than all other injection types (bevacizumab, brolucizumab-dbll, aflibercept, and ranibizumab). This may be due to the fact that eyes treated with bevacizumab are often earlier in the disease course with previously uncontrolled disease; as mentioned above, bevacizumab is often used as a first-line agent. Additionally, as discussed above, patients treated with faricimab often have more severe disease or have failed other agents, and this may explain the shorter duration of treatment seen in patients receiving faricimab, and thus despite having fewer SMH compared to the other cohorts, eyes developing SMH while treated with faricimab are going to bleed regardless of the agent used.

There were 9107 total eyes diagnosed with SMH, representing just over 6% of all eyes being treated in the study.

Other studies have found a similar efficacy and safety profile between aflibercept, ranibizumab, and bevacizumab.[12] Given the potentially devastating effects of SMH, it is important to minimize risks during treatment for nAMD. While all injection types demonstrated a low rate of SMH, faricimab-svoa may be most protective against SMH in the treatment of nAMD. This may be due to faricimab's additional inhibition of angiopoietin-2 (ang2); however, there is scant evidence for anti-ang2 therapy reducing hemorrhage rates, with one case report demonstrating adjunctive therapy with intravitreal faricimab for bilateral choroiditis and occlusive retinal vasculitis complicated by retinal neovascularization and vitreous hemorrhage secondary to intraocular tuberculosis.[19] In a recent meta-analysis of 4 randomized controlled trials, faricimab was found to be noninferior to other anti-VEGF therapies for neovascular AMD and diabetic macular edema.[20] Switching from aflibercept to faricimab has also been shown to allow for extension of treatment from monthly to bimonthly in 40% of eyes in one study[21]; however, this finding may have to be balanced with the shorter interval seen between last faricimab injection to onset of SMH (48.9 days, SD 27.9 days).

The study also examined VA outcomes and surgical management, finding no significant difference between mean VA by injection type before SMH and at 12 months after SMH. Additionally, VA tended to be lower at time of SMH vs at most recent visit before SMH, suggesting that most instances of SMH captured in this dataset were clinically meaningful with an initial decrease in vision. Only 1.7% of eyes in the study database required PPV, suggesting that the vast majority of SMH do not require surgical intervention, although this is limited due to the nature of a retrospective review in which many patients may be coded with an SMH, but this SMH may be extrafoveal and not affecting the VA, in which case many surgeons will opt not to pursue aggressive management strategies. Of those that did require PPV, mean VA improved at 12 months after PPV in each anti-VEGF treatment subgroup. In the context of a recent study demonstrating nonsuperiority of surgery with anti-VEGF injection vs pneumatic displacement with anti-VEGF injection,[11] rates of surgical intervention for SMH may be likely to remain low, with nonoperative management sufficient for many cases of SMH.

Strengths of this study include a large patient population and the ability to examine five different anti-VEGF injection types. Due to the large study size, significant differences were able to be found between anti-VEGF injection types; while the visual significance of these findings remain up for debate, clinically, the appearance of new retinal hemorrhages indicates an insufficient treatment strategy and the need to change injection agents. As anti-VEGF treatments are used both for nAMD and for SMH, more prospective studies are needed to determine superiority of one anti-VEGF treatment over another for minimizing SMH risk.

Limitations include the retrospective nature of the study and data derived from retina private practices only; however, this is unlikely to affect results, as most patients undergoing intravitreal injections for nAMD will be treated by a retina specialist. Confounders, such as antiplatelet use and anticoagulation use, may also exist which affect the data; however, the rates of antiplatelet use and anticoagulation use were similar between injection types (Table 2), minimizing any confounding effects. Another limitation is the lack of data on extent of SMH; instead, the study relies on VA to grossly determine that SMH recorded in the study is, on average, likely clinically significant, but ultimately cannot make a determination on the significance of the hemorrhages included in the database. The study is also limited by lack of data on types of macular neovascularization (Type 1, Type 2, etc.). Finally, this study did not evaluate treatment efficacy for neovascular AMD outcomes such as VA or reduction in macular edema; rather, it evaluated only SMH rates and associated outcomes such as surgical intervention.

Ultimately, while prospective studies will need to be performed to truly establish superiority of any specific anti-VEGF injection over another, given this study's size and statistical significance, the selection of faricimab-svoa may reduce rates of SMH compared to other intravitreal agents, however, this may be a consequence eyes treated with other drugs were being treated for a longer period of time and thus this may be due to progressive disease burden regardless of medication.

PRECIS

In this large-scale database study, six percent of patients with neovascular age-related macular degeneration (nAMD) developed submacular hemorrhage (SMH). Management of SMH and outcomes were limited as both surgical and medical management performing similarly. Faricimab may be more protective than other anti-VEGF injections against SMH development in patients with nAMD.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Gabriel T. Kaufmann: Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis. **Nicholas Boucher:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Chakshu Sharma:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Nitika Aggarwal:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Matthew R. Starr:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

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REFERENCES

1. Avery RL, Fekrat S, Hawkins BS, Bressler NM. Natural history of subfoveal subretinal hemorrhage in age-related macular degeneration. *Retina*. 1996;16(3):183.
2. Scupola A, Coscas G, Soubrane G, Balestrazzi E. Natural history of macular subretinal hemorrhage in age-related macular degeneration. *Ophthalmologica*. 1999;213(2):97–102. doi:10.1159/000027400.
3. Cho JH, Ryoo NK, Cho KH, Park SJ, Park KH, Woo SJ. Incidence rate of massive submacular hemorrhage and its risk factors in polypoidal choroidal vasculopathy. *Am J Ophthalmol*. 2016;169:79–88. doi:10.1016/j.ajo.2016.06.014.
4. Starr MR, Kung FF, Mejia CA, Bui YT, Bakri SJ. Ten-year follow-up of patients with exudative age-related macular degeneration treated with intravitreal anti–vascular endothelial growth factor injections. *Retina*. 2020;40(9):1665. doi:10.1097/IAE.0000000000002668.
5. Starr MR, Xu D, Boucher N, et al. Characterizing progression to neovascular AMD in fellow eyes of patients treated with intravitreal anti-VEGF injections. *Ophthalmic Surg Lasers Imaging Retina*. 2021;52(3):123–128. doi:10.3928/23258160-20210302-02.
6. Matsunaga DR, Su D, Sioufi K, et al. The timing of large submacular hemorrhage secondary to age-related macular degeneration relative to anti–VEGF therapy. *Ophthalmol Retina*. 2021;5(4):342–347. doi:10.1016/j.oret.2020.07.028.
7. Gabrielle PH, Maitrias S, Nguyen V, et al. Incidence, risk factors and outcomes of submacular haemorrhage with loss of vision in neovascular age-related macular degeneration in daily clinical practice: data from the FRB! registry. *Acta Ophthalmol (Copenh)*. 2022;100(8):e1569–e1578. doi:10.1111/aos.15137.
8. Fine HF, Iranmanesh R, Del Priore LV, et al. Surgical outcomes after massive subretinal hemorrhage secondary to age-related macular degeneration. *Retina Phila Pa*. 2010;30(10):1588–1594. doi:10.1097/IAE.0b013e3181e2263c.
9. Hwang JU, Yang SJ, Yoon YH, Lee JY, Kim JG. Recurrent submacular hemorrhage in patients with neovascular age-related macular degeneration. *Retina*. 2012;32(4):652. doi:10.1097/IAE.0b013e318233abb4.
10. Kim KH, Kim JH, Chang YS, Lee TG, Kim JW, Lew YJ. Clinical outcomes of eyes with submacular hemorrhage secondary to age-related macular degeneration treated with antivascular endothelial growth factor. *Korean J Ophthalmol KJO*. 2015;29(5):315–324. doi:10.3341/kjo.2015.29.5.315.
11. Gabrielle PH, Delyfer MN, Glacet-Bernard A, et al. Surgery, tissue plasminogen activator, antiangiogenic agents, and age-related macular degeneration study: a randomized controlled trial for submacular hemorrhage secondary to age-related macular degeneration. *Ophthalmology*. 2023;130(9):947–957. doi:10.1016/j.ophtha.2023.04.014.
12. Iglicki M, Khoury M, Donato L, Quispe DJ, Negri HP, Melamud JI. Comparison of subretinal aflibercept vs ranibizumab vs bevacizumab in the context of PPV, pneumatic displacement with subretinal air and subretinal tPA in naïve submacular haemorrhage secondary to nAMD. "The Submarine Study". *Eye Lond Engl*. 2024;38:292–296. doi:10.1038/s41433-023-02676-9.
13. Kertes PJ, Galic IJ, Greve M, et al. Canadian treat-and-extend analysis trial with ranibizumab in patients with neovascular age-related macular disease: one-year results of the randomized Canadian treat-and-extend analysis trial with ranibizumab study. *Ophthalmology*. 2019;126(6):841–848. doi:10.1016/j.ophtha.2019.01.013.
14. Silva R, Berta A, Larsen M, Macfadden W, Feller C, Monés J. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration: results with ranibizumab from the TREND study. *Ophthalmology*. 2018;125(1):57–65. doi:10.1016/j.ophtha.2017.07.014.
15. Wykoff CC, Croft DE, Brown DM, et al. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. *Ophthalmology*. 2015;122(12):2514–2522. doi:10.1016/j.ophtha.2015.08.009.
16. Gupta OP, Shienbaum G, Patel AH, Fecarotta C, Kaiser RS, Regillo CD. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration: clinical and economic impact. *Ophthalmology*. 2010;117(11):2134–2140. doi:10.1016/j.ophtha.2010.02.032.
17. Engelbert M, Zweifel SA, Freund KB. Long-term follow-up for type 1 (subretinal pigment epithelium) neovascularization using a modified "treat and extend" dosing regimen of intravitreal antivascular endothelial growth factor therapy. *Retina Phila Pa*. 2010;30(9):1368–1375. doi:10.1097/IAE.0b013e3181d50cbf.
18. Levine JP, Marcus I, Sorenson JA, Spaide RF, Cooney MJ, Freund KB. Macular hemorrhage in neovascular age-related macular degeneration after stabilization with antiangiogenic therapy. *Retina Phila Pa*. 2009;29(8):1074–1079. doi:10.1097/IAE.0b013e3181b09443.
19. Alcibahy Y, Julian K, Bonilla MF, Mohamed A, Amrani S, Agarwal A. Intravitreal faricimab as an adjuvant in the management of tubercular uveitis. *Retin Cases Brief Rep*. 2023. A 10.1097/ICB.0000000000001542. doi:10.1097/ICB.0000000000001542.
20. Li G, Zhu N, Ji A. Comparative efficacy and safety of Faricimab and other anti-VEGF therapy for age-related macular degeneration and diabetic macular edema: a systematic review and meta-analysis of randomized clinical trials. *Medicine (Baltimore)*. 2023;102(50):e36370. doi:10.1097/MD.0000000000036370.
21. Kataoka K, Itagaki K, Hashiya N, et al. Six-month outcomes of switching from aflibercept to faricimab in refractory cases of neovascular age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol*. 2024;262(1):43–51. doi:10.1007/s00417-023-06222-x.