Acta Ophthalmologica

Acta Ophthalmologica 2022

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

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ABSTRACT.

Purpose: **The main purpose of the study was to report the estimated incidence, cumulative rate, risk factors and outcomes of submacular haemorrhage (SMH) with loss of vision in neovascular age-related macular degeneration (nAMD) receiving intravitreal injections (IVT) of vascular endothelial growth factor (VEGF) inhibitor in routine clinical practice.**

Methods: **Retrospective analysis of treatment-naïve eyes receiving IVTs of VEGF inhibitors (ranibizumab, aflibercept or bevacizumab) for nAMD from 1 January 2010 to 31 December 2020 that were tracked the Fight Retinal Blindness! registry. Estimated incidence, cumulative rate and hazard ratios (HR) of SMH with loss of vision during treatment were measured using the Poisson regression, Kaplan–Meier survival curves and Cox proportional hazard models.**

Results: **We identified 7642 eyes (6425 patients) with a total of 135 095 IVT over a 10-year period. One hundred five eyes developed SMH with loss of vision with a rate of 1 per 1283 injections (0.08% 95% confidence interval [95% CI] [0.06; 0.09]). The estimated incidence [95% CI] was 4.6 [3.8; 5.7] SMH with loss of vision per year per 1000 treated patients during the study. The cumulative [95% CI] rate of SMH per patient did not increase significantly with each successive injection ($p = 0.947$). SMH cases had a mean VA drop of around 6 lines at diagnosis, which then improved moderately to a 4-line loss at 1 year.**

Conclusions: **Submacular haemorrhage (SMH) with loss of vision is an uncommon complication that can occur at any time in eyes treated for nAMD in routine clinical practice, with only limited recovery of vision 1 year later.**

Key words: AMD – database study – incidence – macular haemorrhage – neovascular age-related macular degeneration – real-world study – risk factors – submacular haemorrhage – VEGF inhibitors

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Gabrielle P-H is supported by an educational grant from *La Fondation de France* research fellowship programme. The FRB registry project was supported by a grant from the Royal Australian NZ College of Ophthalmologists Eye Foundation (2007–2009), a grant from the National Health and Medical Research Council, Australia (NHMRC 2010–2012) and a grant from the Macular Disease Foundation, Australia. Funding was also provided by Novartis and Bayer. These supporting organizations had no role in the design or conduct of the research.

All authors declare that they meet the current ICMJE criteria for authorship. PHG, VN, MG, DB contributed to conception and design; PHG, SM, VN, CCG, MG drafted teh article; PHG, SM, VN, DS, LA, JSM, FV, LO, CCG, MG, JA, DB contributed to data acquisition and final approval of the version to be published.

Acta Ophthalmol.

doi: 10.1111/aos.15137

Introduction

Submacular haemorrhage (SMH), a complication of neovascular age-related macular degeneration (nAMD), can cause severe visual impairment if the fovea is involved (Bennett et al. 1990). It seems to be relatively uncommon, though few studies have reported its incidence over time (Stanescu-Segall et al. 2016). A few studies have investigated risk factors for the development of SMH and have reported favourable outcomes with a range of different treatments, such as intravitreal VEGF (vascular endothelial growth factor) and with pneumatic displacement or surgical vitrectomy with subretinal tPA and pneumatic displacement (Hassan et al. 1999; Haupert et al. 2001; Sandhu et al. 2010; Tognetto et al. 2011; Kapran et al. 2013; Shienbaum et al. 2013; Kim et al. 2014; Shin et al. 2015). More data on incidence, predictors and outcomes of SMH may indicate better ways to prevent and treat them. We aimed to assess the estimated incidence of SMH with loss of vision secondary to nAMD treated with VEGF inhibitors in routine clinical practice. The secondary

objectives were to report baseline risk factors for developing SMH in nAMD-treated eyes, evaluate the 1-year treatment outcomes of SMH eyes compared with matched control eyes and look for predictors of recovery of vision 12 months later.

Methods

Design and setting

This was a retrospective analysis of treatment-naïve eyes that had received intravitreal VEGF inhibitors for nAMD in routine clinical practice tracked in the prospectively designed observational database – the Fight Retinal Blindness! registry (Gillies et al. 2014). Patients participating in this analysis were from Australia, France, Ireland, Italy, Netherlands, New Zealand, Spain, Singapore, Switzerland and United Kingdom. Institutional approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee, the Southern Eastern Sydney Local Health District Human Research Ethics Committee, the French Institutional Review Board (IRB) (Société Française d'Ophtalmologie IRB), IRB of the Mater Private Hospital in Dublin, the IRCCS Cà Granda Foundation Maggiore Policlinico Hospital Milan IRB, the Caldicott Guardian at the Royal Free London NHS Foundation Trust, the SingHealth Singapore, the Clinical Research Ethics Committee of Aragon (Spain) and the Cantonal Ethics Committee Zurich. Due to its non-interventional character, approval of the use of the registry was not needed according to the Medical Ethics Committee of the Academic Medical University Centre, the Netherlands. All patients gave their informed consent. Informed consent ('opt-in consent') was sought from patients in France, Ireland, Italy, Netherlands, Spain, Singapore, Switzerland and United Kingdom. Ethics committees in Australia and New Zealand approved the use of 'opt-out' patient consent. This study adhered to the tenets of the Declaration of Helsinki.

Data sources and measurements

We analysed data from the AMD module of the FRB! outcomes registry. Data were obtained from each visit, including the VA (best of corrected uncorrected and pinhole), the activity of the underlying choroidal neovascularization (CNV) lesion, treatment given, procedures and ocular adverse events. VA scores were converted as the number of letters read on a logarithm of the minimum angle of resolution (logMAR) VA standard ETDRS chart (Dong et al. 2003). The activity of the CNV lesion (active or inactive) was graded by the treating physician based on findings from clinical examination according to a definition provided in the data collection screen from optical coherence tomography (OCT) and dye-based fundus fluorescein angiography, alone or in combination, at each visit. Demographic characteristics (age and gender), the type and greatest linear diameter of the CNV (based on baseline dye-based angiography) and whether the eye received prior treatment for the condition being audited were recorded at baseline visit. Treatment decisions, including the choice of VEGF inhibitor and visit schedule, were at the discretion of the physician in consultation with the patient, thereby reflecting daily clinical practice.

'Hemorrhage reducing VA>15 letters' can be chosen when appropriate from the drop-down menu of the forced choice (yes/no) adverse event field that appears at each visit in the FRB! nAMD module. Each case was audited by sending a questionnaire to participating ophthalmologists. Eyes were excluded if any other cause of haemorrhage were present such as vitreous haemorrhage or other retinal cause such as retinal arterial microaneurysm, diabetic retinopathy, vasculitis or other vascular abnormalities. We also asked participating ophthalmologists to report the clinical and multimodal imaging characteristics of the SMH at diagnosis, initial management and time to procedure.

The VA at SMH was defined as the VA during the visit SMH was recorded while the VA prior SMH was defined as the VA in the visit immediately before the SMH visit. The VA loss (change) at SMH, which indicated the immediate impact of the SMH, was calculated as the VA at SMH minus the VA prior SMH. The 1-year VA loss (change) from prior SMH was defined as the VA 1 year after the SMH (or last recorded visit if they did not complete 1 year of follow-up) minus VA prior SMH to calculate the permanent vision loss, if any, resulting from the SMH. The 1-year VA loss (change) from SMH was considered as the VA 1 year after the SMH (or last recorded visit) minus VA at SMH to assess the recovery from the SMH.

Patient selection and groups

Treatment-naive eyes tracked by the FRB! outcome registry that started intravitreal therapy (IVT) with VEGF inhibitors (ranibizumab [0.5 mg Lucentis, Genetech Inc/Novartis], aflibercept [2 mg Eylea, Regeneron Inc/Bayer] or bevacizumab [1 mg Avastin, Genetech Inc/Roche]) for neovascular age-related macular degeneration (nAMD) from 1 January 2010 to 31 December 2020 were considered for the analysis.

Eyes with SMH were partitioned according to the initial management at the time of SMH diagnosis. *Conservative management* was defined as eyes initially managed with intravitreal injection of VEGF inhibitor alone. *Pneumatic displacement management* was defined as eyes initially managed with a combination of intravitreal injections of VEGF inhibitor and tPA associated with pneumatic displacement. *Surgical management* was defined as eyes initially managed with a combination of vitrectomy, subretinal tPA and an intravitreal VEGF inhibitor with pneumatic displacement. There were no specific management protocols, so the management decision at SMH was determined by the physician based on symptoms, VA and multimodal imaging in consultation with the patient.

We used a matched cohort consisting of 5 controls (defined as eyes that did not develop SMH with loss of vision during treatment) per case matched on the following characteristics: baseline age, gender, baseline VA, time duration of follow-up, VA prior to SMH, baseline type of CNV lesion and the number of IVTs before SMH.

Outcomes

The main outcome was the estimated incidence of SMH with loss of vision over the study period. Secondary outcomes were the cumulative rate of

SMH and factors that predicted the development of SMH. Other outcomes of interest were the visual and treatment outcomes at 12 months after SMH, including comparisons between cases versus matched controls and between types of initial management. We also assessed baseline clinical and imaging functional predictive factor of prior SMH VA recovery at 1 year.

All cases of SMH with loss of vision were recorded regardless of their follow-up in order to study the estimated incidence, cumulative rate and hazard ratios. For outcomes after diagnosis of SMH, SMH had to have occurred before 31 December 2019 to allow at least 1 year of follow-up. Eyes that completed at least 335 days of follow-up after SMH were defined as 'completers'. The 'non-completers' were defined as eyes who did not complete at least 335 days of follow-up after SMH.

Statistical analysis

Descriptive data were summarized using the mean (standard deviation), median (first and third quartiles) and percentages where appropriate. The estimated incidence of SMH per year per 1000 patients and per 10 000 injections during the study period were evaluated using the Poisson test. Kaplan–Meier curves were used to visualize the cumulative rate of SMH by number of injections received and length of follow-up. Cox proportional hazards models were used to relate SMH development to the following covariates: baseline age, gender, baseline VA, type and size of CNV lesion at baseline and the type of VEGF inhibitor.

Locally weighted scatterplot smoothing (LOESS) regression was used to visualize longitudinal visual outcomes over 12 months between SMH case eyes and matched control eyes. Visual and treatment outcomes were compared between SMH case eyes and matched control eyes using ANOVA, t-tests and chi-square tests where appropriate.

The proportion of eyes recovering their pre-SMH vision at 12 months was analysed using logistic mixed-effects regression. The main predictors investigated using univariate analysis were age, gender, baseline SMH clinical and OCT imaging characteristics and type of initial management. The final multivariate regression model was adjusted for significant univariate factors as fixed effects and nesting of outcomes within practitioners and patients with bilateral disease as random effects.

A p-value of 0.05 was considered statistically significant. p-values from pairwise comparisons were adjusted for using the Holm–Bonferroni correction method. All analyses were conducted using R software version 4.1.0 (http://www.R-project.org/).

Results

Study population

This study included 7642 eyes (6425 patients) treated between 1 January 2010 and 31 December 2020 receiving 135095 IVTs overall. The number of eyes at each selection criterion is shown in Fig. S1. Nineteen per cent of eligible eyes completed at least 5 years of follow-up. One hundred five eyes developed SMH with loss of vision during the study period, of which 95 eyes developed it before 31 December 2019 and were therefore able to have at least 12 months of follow-up from the onset of SMH. Seventy-three eyes (76%) completed 12 months follow-up after the SMH. Audit questionnaires were obtained for 55 out of 95 (58%) SMH cases.

Incidence and rate of SMH

The estimated incidence of SMH with loss of vision (95% confidence interval [95% CI]) per year per 1000 patients and per 10 000 injections was 4.6 (3.8, 5.6) and 7.8 (6.4, 9.4) respectively (Table 1). SMH with loss of vision tended to be more frequent in eyes with polypoidal choroidal vasculopathy than eyes with other types of CNV (Table 1).

Kaplan–Meier curves showing the cumulative rate of SMH with loss of vision by length of follow-up and number of injections are shown in Fig. 1A,B. The cumulative rate of SMH was 1.1% at 2 years, 1.7% at 4 years, 2.5% at 6 years, 3.2% at 8 years and 4.4% at 10 years of follow-up (Fig. 1A). The cumulative rate of SMH was 0.95% at 10 injections, 1.62% at 20 injections, 2.12% at 30 injections, 2.59% at 40 injections and 3.01% at 50 injections. We did not find any clinically significant increase in the probability of SMH with each successive injection, even after more than 50 injections ($p = 0.947$). Thus, each successive injection without a SMH did not seem to increase the risk of developing a SMH at the next injection (Table 1 and Fig. 1B). The median (Q1, Q3) time and injections until SMH were 890 (395, 1573) days and 13 (7, 23) injections (Table 1).

Cox proportional hazards model was used to identify baseline covariates that predicted development of SMH with loss of vision in eyes receiving VEGF inhibitors for nAMD (Table 2). Males (hazard ratio [HR] [95% CI] = 1.71 [1.26, 2.16] versus females; $p = 0.019$) were more likely to develop SMH over the study (Table 2). That is, the likelihood of developing SMH increased by 71% if the patient was male at the start of the treatment. Age, presenting VA and baseline angiographic size of the CNV lesion were not significantly associated with SMH development, nor was the type of VEGF inhibitor prior to SMH (HR = 0.89 [0.15, 1.93] for aflibercept and 1.06 [0.09, 2.03] for ranibizumab versus bevacizumab [reference]; $p = 0.87$) (Table 2). Baseline type of CNV tended to be significantly associated with SMH development (Global $p = 0.047$); however, after adjustment for multiple comparisons, only eyes with disciform scars at baseline had a significantly increased risk of SMH (HR = 12.35 [10.76, 13.94]; $p = 0.002$) than eyes with type 1 CNV (Table 2).

Treatment and CNV activity characteristics before SMH diagnosis were similar between SMH with loss of vision and their matched controls (Table 3). Sixty per cent of SMH cases and controls had their last injection less than 60 days before the development of SMH with loss of vision. The CNV lesions of eyes that developed SMH tended to be more frequently graded as active at the last visit before it developed than their matched controls (48% versus 36%; $p = 0.10$ respectively) (Table 3).

One-year outcomes of SMH compared to controls

The visual outcomes of SMH cases compared with matched control eyes

Table 1. Incidence and cumulative rate of submacular haemorrhage over the study period.

	Submacular haemorrhage
Cases, *n*	105
Study period, year	10
Injections over the study period, *n*	135 095
Patients, *n*	6425
Females, *n* (%)	3915 (61)
Age, mean year (SD)	80 (9)
Incidence per year per 1000 patients (95% CI)*	4.6 (3.8, 5.6)
Incidence per 10 000 injections (95% CI)*	7.8 (6.4, 9.4)
Cases and rate by type of VEGF inhibitors, case/injections (%)†	
Bevacizumab	29/13 775 (0.21)
Ranibizumab	50/63 067 (0.08)
Aflibercept	26/58 253 (0.04)
Cumulative rate per patient following number of injections %‡	
10th injection	0.95
20th injection	1.63
30th injection	2.12
40th injection	2.59
50th injection	3.01
Case and rate by type of choroidal neovascularization lesion, case/injections (%)§	
Type 1	59/88 499 (0.07)
Type 2	19/29 903 (0.06)
Type 3	7/8684 (0.08)
Polypoidal choroidal vasculopathy	15/4869 (0.31)
Peripapillary choroidal neovascularization	3/2669 (0.11)
Disciform scar	2/471 (0.42)
Time (days) to SMH, median (Q1, Q3)	890 (395, 1573)
Number of injections until submacular haemorrhage, median (Q1, Q3)	13 (7, 23)
Time between last injection and SMH days, mean (SD)	17 (43)
Last injection ≥90 days before SMH, *n* (%)	6 (5.7)

CI = confidence interval, *n* = number, Q1 = first quartile, Q3 = third quartile, SD = standard deviation, VEGF = vascular endothelial growth factor.

* Calculated using the Poisson test.

† Type of VEGF inhibitor received before diagnosis of submacular haemorrhage (SMH) ($p < 0.01$); Pairwise comparisons with false discovery rate adjustment for multiple comparisons: Bevacizumab versus Ranibizumab ($p < 0.01$), Ranibizumab versus Aflibercept ($p = 0.023$), Bevacizumab versus Aflibercept ($p < 0.01$).

‡ The cumulative rate of SMH per patient did not increase significantly with each successive injection ($p = 0.947$).

§ p-value among the types of choroidal neovascularization lesion ($p < 0.01$); pairwise comparisons with false discovery rate adjustment for multiple comparisons: Type 1 versus polypoidal choroidal vasculopathy ($p < 0.01$), Type 2 versus polypoidal choroidal vasculopathy ($p < 0.01$), Type 3 versus polypoidal choroidal vasculopathy ($p = 0.017$), other group comparisons ($p > 0.05$).

are described in Fig. 2 and Table 3. Mean (95% CI) change in VA from prior SMH was −20 (−26, −15) letters 12 months after SMH. Sixty and fifty-three per cent of SMH eyes had at least a 2-line and 3-line loss of vision from prior SMH at 12 months respectively. A quarter of SMH eyes recovered their VA prior SMH at 12 months, while half of matched control eyes maintained their vision during the same period ($p < 0.01$) (Table 3). There was no significant difference in the median number of treatments and visits between cases and matched controls at 12 months (Table 3).

Predictors of visual recovery and visual outcomes according to initial management

An audit questionnaire of 55 SMH cases (58% of the SMH cohort) collecting baseline clinical and imaging SMH characteristics and initial management (conservative, pneumatic displacement or surgery) was obtained. Table 4 summarizes the predictive factors for visual recovery at 12 months. SMH cases with better VA at the last visit prior SMH tended to be less likely to recover their prior VA at 1 year (univariate odds ratio [OR] [95% CI] = 0.98 [0.95, 1.00] per letter; $p = 0.040$), though this was not found statistically significant by the multivariate logistic regression model (OR [95% CI] = 1.02 [1.00, 1.05] per letter; $p = 0.0504$) (Table 4). Eyes that had additional initial treatment, such as pneumatic displacement or surgery, did not seem to have better outcomes at 1 year than eyes that continued with

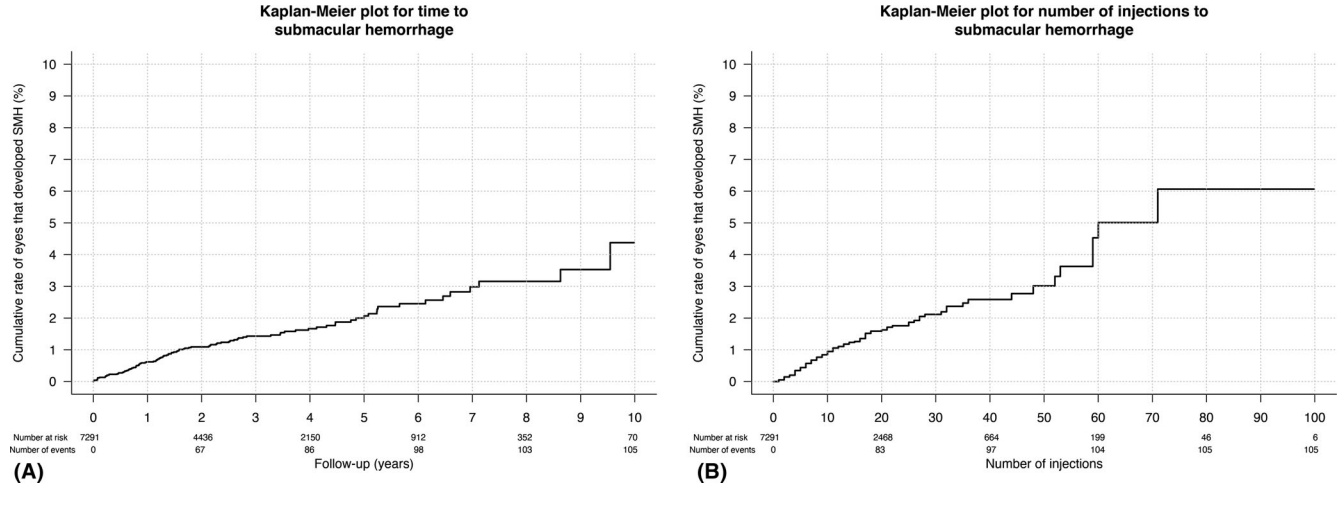

Fig. 1. Kaplan–Meier curve of the cumulative rate of submacular haemorrhage by (A) length of follow-up and (B) number of injections received.

Table 2. Mixed-effects Cox proportional hazard regression model for development of submacular haemorrhage.

	Development of submacular haemorrhage	
Covariates (reference if categorical)	Hazard ratio (95% CI)	p-value
Gender (female)		**0.019**
Male	1.71 (1.26, 2.16)	
Age at baseline (every 10 years of age)	1.17 (0.90, 1.45)	0.26
Visual acuity at baseline (every 10-letter score)	0.97 (0.85, 1.10)	0.63
Angiographic CNV lesion size at baseline (small [<500 μm])		0.49
Medium (≥500 μm and ≤1000 μm)	2.82 (0.77, 4.88)	
Large (>1000 μm)	2.58 (0.58, 4.58)	
Type of CNV lesion size at baseline (type 1)		**0.047***
Type 2	0.81 (0.17,1.46)	
Type 3	0.75 (0.02, 1.75)	
Polypoidal choroidal vasculopathy (PCV)	2.19 (1.35, 3.04)	
Peripapillary choroidal neovascularization (PCN)	1.41 (0.19, 2.62)	
Disciform scar	12.35 (10.76, 13.94)	
Type of VEGF inhibitors (bevacizumab)		0.87
Aflibercept	0.89 (0.15, 1.93)	
Ranibizumab	1.06 (0.09, 2.03)	

Model random effects	Standard deviation	Variance
Practitioner/Patient	0.68	0.46
Practitioner	0.93	0.87

95% CI, 95% confidence interval.
p-values are highlighted in bold.
* Global p-value. Pairwise comparisons with Holm–Bonferroni adjustment for multiple comparisons: Type 1 versus Type 2 (p = 0.53), Type 1 versus Type 3 (p = 0.58), Type 1 versus PCV (p = 0.067), Type 1 versus PCN (p = 0.58), Type 1 versus Disciform scar (p = 0.002).

intravitreal VEGF inhibitor monotherapy (Table 4 and Table S1).

Discussion

This FRB! observational database analysis assessed the incidence, cumulative rate, risk factors and 12-month outcomes of SMH with loss of vision over 10 years in nAMD eyes treated with VEGF inhibitors in daily practice. The estimated incidence of SMH with loss of vision was approximately 8 per 10 000 IVTs and 5 per year per 1000 nAMD patients treated with VEGF inhibitors in routine clinical practice.

Few studies have investigated the incidence and rate of this uncommon and potentially severe complication of nAMD. A nationwide prospective observational study using SOSU (Scottish Ophthalmic Surveillance Unit) found an overall incidence of 5.4 SMH (defined as all newly diagnosed cases of fovea-involving SMH of size >2 disc diameters) per million *per annum* (Al-Hity et al. 2019). In relation to the number of patients with exudative AMD (about 1.4% of the population of Europe), this rate (about 5.4 per 14 000 versus 64 per 14 000 in our study) is somewhat lower than in our study (Li et al. 2020). A retrospective study of eyes treated with ranibizumab IVT for nAMD found a relatively higher rate with 8% of newly developed or increased macular haemorrhage (retinal and subretinal, defined as a new macular haemorrhage greater than 200 mm within 1 disc diameter of the foveal centre or an increase in size greater than 200 mm within the temporal vascular arcades) at 1 month of the first injection (Moon et al. 2013). Neither study considered VA in their definition as we did.

It is important to describe the cumulative rate per patient when evaluating the risk of a complication and to compare results between reports since treatment frequency and length of follow-up may vary between patients and in different studies. The cumulative rate of SMH per patient increased linearly with time and the number of injections in our study. We were reassured to find there was no exponential increase in the rate of SMH with each successive injection, even after more than 50 injections (p = 0.95), but nor did the risk of SMH decrease with time.

Of clinical interest, we found that men and eyes with disciform scar CNV type at baseline were much more likely to develop SMH in our study. Previous studies have reported that eyes with larger CNV lesion treated with VEGF inhibitors were more likely to develop SMH (Goverdhan & Lochhead 2008; Krishnan et al. 2009). The multiple transient CNV membrane contractions and extensions when treated with VEGF inhibitors could lead to an increased risk of new vessels rupturing and bleeding, especially in large fibrotic CNV lesions. No previous study has reported that men were at an increased risk of SMH. This finding should be taken cautiously and warrants replication in further studies. Several studies have already shown that PCV is an important cause of SMH, notably in Asian patients (Corvi et al. 2022, Kunavisarut et al. 2018, Sho et al. 2003). Our study had relatively few eyes with PCV since our population was mostly of Caucasian ethnicity (97% versus 2% of Asian). Interestingly, the risk of SMH did not seem to be influenced by the type of VEGF inhibitors confirming that all type of VEGF inhibitors have similar treatment outcomes for nAMD in routine clinical practice (Gillies et al. 2015; Bhandari et al. 2020; Lestable et al. 2020). Additionally, treatment and activity characteristics at the visit before SMH developed were similar between SMH cases and their matched controls. SMH cases more often had active CNV lesions at the last visit prior to SMH than their controls, but this difference was not statistically significant. The last IVT interval was similar between both groups with more than 20% of eyes having their last IVT more than 3 months in each group, which also suggests that the time interval between IVT did not seem to influence the risk of SMH with loss of vision. Under-treatment did not appear to be a significant cause of SMH with loss of vision in this analysis, which corroborate recent data (Matsunaga et al. 2020). Although the mechanism remains unknown, it has been hypothesized that SMH could develop independently of VEGF suppression level by vascular rupture due to tangential

Table 3. Treatment and visual outcomes before and after submacular haemorrhage compared with matched control group without submacular haemorrhage.

	SMH case	Matched control*	p
Eyes, *n*	95	475	
Treatment and CNV activity characteristics before SMH			
Time since last injection days, median (Q1, Q3)	50 (29, 84)	49 (35, 83)	0.29
Last injection < 60 days, %	58	60	0.11
Last injection ≥ 60 days, %	42	40	0.74
Last injection ≥ 90 days, %	24	20	0.50
CNV Activity graded as active at last visit before SMH, %	48	36	0.10
Time since last visit graded as active days, mean (SD)	171 (228)	134 (261)	0.23
Visual acuity letters, mean (SD)			
Baseline	59 (17)	60 (16)	0.64
Prior SMH	61 (19)	63 (18)	0.32
At SMH	30 (22)	63 (18)	**<0.01**
Final (at 12 months from SMH)†	41 (27)	63 (18)	**<0.01**
Visual acuity change at SMH letters, mean (95% CI)	−31 (22)	-	**<0.01**
Visual acuity change from SMH at 12 months letters, mean (95% CI)	11 (6, 15)	0 (−1, 1)	**<0.01**
Visual acuity gain from SMH at 12 months, %			
≥5 letters	55	27	**<0.01**
≥10 letters	47	14	**<0.01**
≥15 letters	42	7	**<0.01**
Visual acuity change from prior SMH at 12 months letters, mean (95% CI)	−20 (−26, −15)	0 (−1, 1)	**<0.01**
Visual acuity loss from prior SMH at 12 months, %			
<5 letters	31	71	**<0.01**
≥5 letters	70	29	**<0.01**
≥10 letters	60	14	**<0.01**
≥15 letters	53	7	**<0.01**
Visual acuity recorded prior SMH recovered at 12 months, %	23	54	**<0.01**
Injections 12 months after SMH, median (Q1, Q3)	7 (3, 9)	6 (4, 8)	0.98
Visits 12 months after SMH, median (Q1, Q3)	9 (7, 11)	9 (7, 11)	0.93

95% CI = 95% confidence interval, *n* = number, Q1 = first quartile, Q3 = third quartile, SD = standard deviation, SMH = submacular haemorrhage.
Significant p-values are highlighted in bold.
* Control groups are matched for age, gender, time of follow-up, VA prior SMH, number of injections at SMH, baseline type of CNV.
† Last observation carried forward for non-completers.

stress following CNV contraction, which had been similarly described in acute RPE tears occurring after injection (Matsunaga et al. 2020).

Our report emphasizes the poor visual prognosis of eyes developing SMH secondary to nAMD, with only a quarter of cases recovering their VA prior to SMH at 12 months. Although the mean VA improved with treatment by two lines at 1 year from the time of SMH diagnosis, most cases lost ≥3 lines of VA from VA prior to SMH at 1 year in our study, which is consistent with previous reports (Bennett et al. 1990; Avery et al. 1996; Hassan et al. 1999). Additionally, eyes with better VA prior to developing SMH tended to be less likely to recover their prior SMH VA at 1 year.

Several treatments and surgical procedures combined with VEGF inhibitors have been developed that aim to enhance visual recovery after SMH by removing or displacing the blood (Hassan et al. 1999; Sandhu et al. 2010). Physical displacement of the SMH out of the fovea using gas may speed visual recovery and prevent irreversible blood-induced damage to the outer retina. Several studies show that anti-VEGF monotherapy alone was effective in treating SMH secondary to nAMD (Shienbaum et al. 2013; Kim et al. 2014). However, there have been reports of an additional benefit of pneumatic gas displacement with intravitreal tPA or vitrectomy with subretinal tPA and pneumatic displacement, notably for extensive or thicker SMH (Haupert et al. 2001; Tognetto et al. 2011; Kapran et al. 2013). The cases that had additional pneumatic displacement or surgery in the present study did not seem to have better outcomes 1 year later than eyes treated with VEGF inhibitors alone. It is difficult to conclude whether there was any additional benefit of pneumatic displacement or surgical vitrectomy for the initial management of SMH from our retrospective analysis without randomized management allocation.

The strength of this study is that it provides additional real-world data on the incidence, risk factors and long-term outcomes of SMH with loss of vision in nAMD. The FRB! system includes quality assurance measures that eliminate out-of-range and missing data (Gillies et al. 2014). Our study reported treatment outcomes of SMH up to 12 months compared with matched controls.

We acknowledge some weaknesses that are inherent in observational studies. First, the estimated incidence may be underestimated due to information bias since cases were self-reported. Second, there was a lack of randomization of initial management and treatment decisions were made without a study protocol. The selection of cases and management may differ among physicians and the reasons cannot be known from our data. Furthermore, we were only able to obtain these additional data on initial SMH management for 58% of our cases. The FRB system did not collect systemic conditions and medications, notably antithrombotic agents, which may have influenced SMH development and outcomes. Duration of symptoms was also not collected in the FRB database, which is a significant visual prognosis factor in the treatment of SMH. Nevertheless, we reported outcomes of SMH with loss of vision as it is being managed in daily practice.

To conclude, SMH is an uncommon complication in eyes treated with VEGF inhibitors for nAMD in routine clinical practice. Men and eyes with disciform scar CNV type at baseline were at a greater risk of developing SMH on treatment. Although they improved with treatment from the time of SMH, visual outcomes were poor with half of the cases losing at least 3 lines of vision 1 year later.

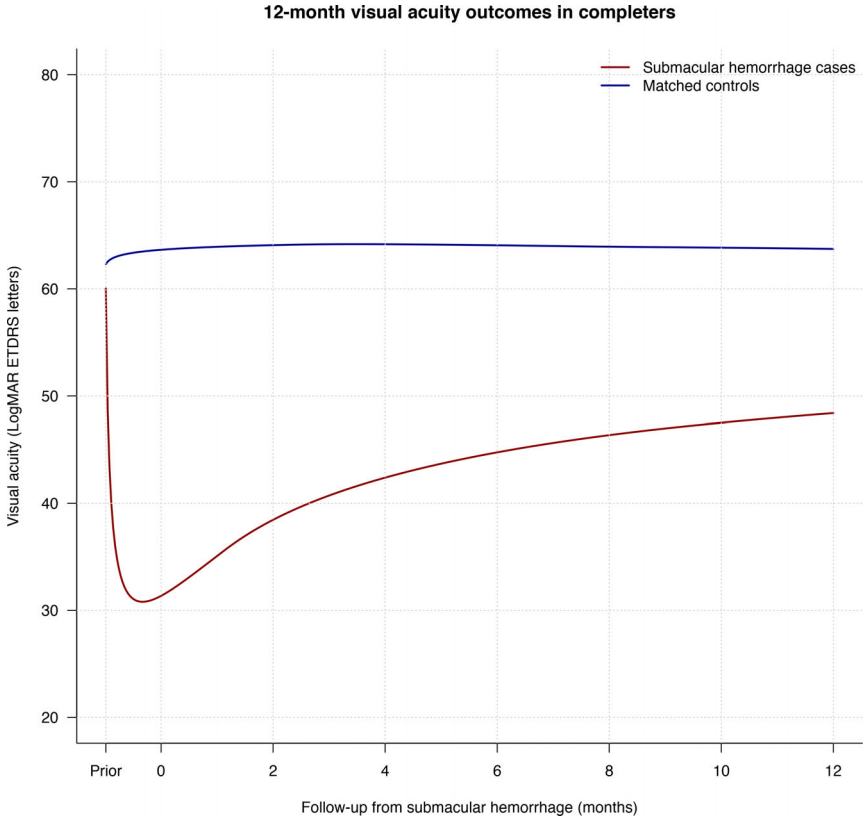

Fig. 2. Locally weighted scatterplot smoothing (Loess) curves regression of mean visual acuity (VA) After onset of submacular haemorrhage (SMH). Matched cohort consisting of 5 controls per case matched with their respective cases on the following characteristics: baseline VA, baseline age, gender, time duration before SMH, last VA recorded before SMH, the number of intravitreal injections before SMH and baseline type of choroidal neovascularization lesion.

Table 4. Results from univariate and multivariate logistic regression models for the proportion of eyes that recovered visual acuity prior SMH at 12 months.

	Recovered VA prior SMH at 12 months			
	Univariate analysis		Multivariate analysis*	
Predictors (reference group for categorical variables)	OR (95% CI)	p	OR (95% CI)	p
Age, per year	1.01 (0.96, 1.06)	0.77	1.02 (0.97, 1.08)	0.39
Gender (female)				
Male	1.43 (0.55, 3.73)	0.46	1.80 (0.65, 4.98)	0.25
VA at last visit prior SMH, per letters	0.98 (0.95, 1.00)	0.040	1.02 (1.00, 1.05)	0.0504
VA at SMH diagnosis, per letters	1.02 (1.00, 1.04)	0.08	–	
Fundus characteristics of the SMH				
Foveal involvement (extrafoveal)		0.66		
Subfoveal	0.59 (0.05, 6.37)		–	
Extension of SMH, (small, ≤ 5-disc area)		0.80		
Large (>5-disc area)	0.83 (0.21, 3.29)		–	
Imaging characteristics of the SMH		0.17		
Central macular thickness, per microns	1.00 (0.99, 1.00)		–	
Thickness of the clot (small, <500 μm)		0.59		
Medium (500–1000 μm)	1.69 (0.34, 8.31)		–	
Large (>1000 μm)	0.50 (0.05, 4.73)		–	
Retinal layer involvement, (Subretinal)		0.28		
SubRPE	3.00 (0.16, 57.36)		–	
Mix of subretinal and subRPE	0.41 (0.10, 1.77)		–	
Type of CNV (Type 1)		0.88		
Type 2	0.63 (0.16, 2.53)		–	
Type 3	0.53 (0.06, 4.78)		–	

Table 4 (Continued)

	Recovered VA prior SMH at 12 months			
	Univariate analysis		Multivariate analysis*	
Predictors (reference group for categorical variables)	OR (95% CI)	p	OR (95% CI)	p
Polypoidal choroidal vasculopathy	1.18 (0.27, 5.12)		–	
Peripapillary CNV	1.58 (0.13, 18.83)		–	
Disciform scar	3.15 (0.18, 54.04)		–	
Initial management (conservative management)		0.76		
Pneumatic or surgical management	0.77 (0.14, 4.20)		–	

CI = confidence interval, OR = odds ratio, SMH = submacular haemorrhage.
Pairwise comparison with Holm–Bonferroni adjustment for multiple comparisons.
* Calculated from logistic mixed-effects regression model adjusting for age, gender and VA at last visit prior SMH.

Ethics Approval

Institutional approval was obtained from the Royal Australian and New Zealand College of Ophthalmologists Human Research Ethics Committee, the Southern Eastern Sydney Local Health District Human Research Ethics Committee, the French Institutional Review Board (IRB) (Société Française d'Ophtalmologie IRB), IRB of the Mater Private Hospital in Dublin, the IRCCS Cà Granda Foundation Maggiore Policlinico Hospital Milan IRB, the Caldicott Guardian at the Royal Free London NHS Foundation Trust, the SingHealth Singapore, the Clinical Research Ethics Committee of Aragon (Spain) and the Cantonal Ethics Committee Zurich. Due to its non-interventional character, approval of the use of the registry was not needed according to the Medical Ethics Committee of the Academic Medical University Centre, the Netherlands. All patients gave their informed consent. Informed consent ('opt-in consent') was sought from patients in France, Ireland, Italy, Netherlands, Spain, Singapore, Switzerland and United Kingdom. Ethics committees in Australia and New Zealand approved the use of 'opt-out' patient consent. This study adhered to the tenets of the Declaration of Helsinki.

References

Al-Hity A, Steel DH, Yorston D, Gilmour D, Koshy Z, Young D, Hillenkamp J & McGowan G (2019): Incidence of submacular haemorrhage (SMH) in Scotland: a Scottish Ophthalmic Surveillance Unit (SOSU) study. Eye (Lond) **33**: 486–491.

Avery RL, Fekrat S, Hawkins BS & Bressler NM (1996): Natural history of subfoveal subretinal hemorrhage in age-related macular degeneration. Retina **16**: 183–189.

Bennett SR, Folk JC, Blodi CF & Klugman M (1990): Factors prognostic of visual outcome in patients with subretinal hemorrhage. Am J Ophthalmol **109**: 33–37.

Bhandari S, Nguyen V, Arnold J, Young S, Banerjee G, Gillies M & Barthelmes D (2020): Treatment outcomes of ranibizumab versus aflibercept for neovascular age-related macular degeneration. Ophthalmology **127**: 369–376.

Corvi F, Chandra S, Invernizzi A et al. (2022): Multimodal imaging comparison of polypoidal choroidal vasculopathy between Asian and Caucasian population. Am J Ophthalmol **234**: 108–116.

Dong LM, Marsh MJ & Hawkins BS (2003): Measurement and analysis of visual acuity in multicenter randomized clinical trials in the United States: Findings from a survey. Ophthalmic Epidemiol **10**: 149–165.

Gillies MC, Campain A, Barthelmes D et al. (2015): Long-term outcomes of treatment of neovascular age-related macular degeneration: data from an observational study. Ophthalmology **122**: 1837–1845.

Gillies MC, Walton R, Liong J et al. (2014): Efficient capture of high-quality data on outcomes of treatment for macular diseases: the fight retinal blindness! Project. Retina (Philadelphia, Pa) **34**: 188–195.

Goverdhan SV & Lochhead J (2008): Submacular haemorrhages after intravitreal bevacizumab for large occult choroidal neovascularisation in age-related macular degeneration. Br J Ophthalmol **92**: 210–212.

Hassan AS, Johnson MW, Schneiderman TE, Regillo CD, Tornambe PE, Poliner LS, Blodi BA & Elner SG (1999): Management of submacular hemorrhage with intravitreous tissue plasminogen activator injection and pneumatic displacement. Ophthalmology **106**: 1900–1906 discussion 1906-1907.

Haupert CL, McCuen BW, Jaffe GJ, Steuer ER, Cox TA, Toth CA, Fekrat S & Postel EA (2001): Pars plana vitrectomy, subretinal injection of tissue plasminogen activator, and fluid-gas exchange for displacement of thick submacular hemorrhage in age-related macular degeneration. Am J Ophthalmol **131**: 208–215.

Kapran Z, Ozkaya A & Uyar OM (2013): Hemorrhagic age-related macular degeneration managed with vitrectomy, subretinal injection of tissue plasminogen activator, gas tamponade, and upright positioning. Ophthalmic Surg Lasers Imaging Retina **44**: 471–476.

Kim JH, Chang YS, Kim JW, Kim CG, Yoo SJ & Cho HJ (2014): Intravitreal anti-vascular endothelial growth factor for submacular hemorrhage from choroidal neovascularization. Ophthalmology **121**: 926–935.

Krishnan R, Goverdhan S & Lochhead J (2009): Submacular haemorrhage after intravitreal bevacizumab compared with intravitreal ranibizumab in large occult choroidal neovascularization. Clin Experiment Ophthalmol **37**: 384–388.

Kunavisarut P, Thithuan T, Patikulsila D, Choovuthayakorn J, Watanachai N, Chaikitmongkol V, Pathanapitoon K & Rothova A (2018): Submacular hemorrhage: visual outcomes and prognostic factors. Asia Pac J Ophthalmol (Phila) **7**: 109–113.

Lestable L, Gabrielle PH, Bron AM, Nguyen P & Creuzot-Garcher C (2020): Twelve-month outcomes of intra-vitreal anti-VEGF agents for treatment-naïve neovascular age-related macular degeneration eyes: French data from the fight for retinal blindness! J Fr Ophtalmol **43**: 761–769.

Li JQ, Welchowski T, Schmid M, Mauschitz MM, Holz FG & Finger RP (2020): Prevalence and incidence of age-related macular degeneration in Europe: a systematic review and meta-analysis. Br J Ophthalmol **104**: 1077–1084.

Matsunaga DR, Su D, Sioufi K, Obeid A, Wibbelsman T, Ho AC & Regillo CD (2020): The timing of large submacular hemorrhage secondary to age-related macular degeneration relative to anti–VEGF therapy. Oph Retina **5**: 342–347.

Moon SW, Oh J, Yu HG, Cho HY & Song SJ (2013): Incidence and risk factors for macular hemorrhage following intravitreal ranibizumab injection for neovascular age-related macular degeneration. J Ocul Pharmacol Ther **29**: 556–559.

Sandhu SS, Manvikar S & Steel DHW (2010): Displacement of submacular hemorrhage associated with age-related macular degeneration using vitrectomy and submacular tPA injection followed by intravitreal ranibizumab. Clin Ophthalmol **4**: 637–642.

Shienbaum G, Garcia Filho CAA, Flynn HW, Nunes RP, Smiddy WE & Rosenfeld PJ (2013): Management of submacular hemorrhage secondary to neovascular age-related macular degeneration with anti-vascular endothelial growth factor monotherapy. Am J Ophthalmol **155**: 1009–1013.

Shin JY, Lee J-M & Byeon SH (2015): Anti-vascular endothelial growth factor with or without pneumatic displacement for submacular hemorrhage. Am J Ophthalmol **159**: 904–914.e1.

Sho K, Takahashi K, Yamada H et al. (2003): Polypoidal choroidal vasculopathy: incidence, demographic features, and clinical characteristics. Arch Ophthalmol **121**: 1392–1396.

Stanescu-Segall D, Balta F & Jackson TL (2016): Submacular hemorrhage in neovascular age-related macular degeneration: a synthesis of the literature. Surv Ophthalmol **61**: 18–32.

Tognetto D, Skiadaresi E, Cecchini P & Ravalico G (2011): Subretinal recombinant tissue plasminogen activator and pneumatic displacement for the management of subretinal hemorrhage occurring after anti-VEGF injections for wet AMD. Clin Ophthalmol **5**: 459–463.

Received on January 18th, 2022.
Accepted on March 12th, 2022.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Flow chart showing the number of eyes remaining at each selection criterion.

Table S1 12-month outcomes of audited SMH eyes and according to initial management at diagnosis of the submacular haemorrhage.