

**Title:** Incidence of submacular haemorrhage (SMH) in Scotland: a Scottish Ophthalmic Surveillance Unit Study (SOSU) study

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**Purpose:** Submacular haemorrhage is a cause of severe visual loss in neovascular age-related macular degeneration (nAMD). The incidence is uncertain and furthermore there is no widely-used classification system nor agreed best practice. The aim of this national surveillance study was to identify the incidence, presenting features and clinical course of new fovea-involving submacular haemorrhage associated with nAMD.

**Method:** A questionnaire was sent monthly to every ophthalmic specialist in Scotland over a 12-month period asking them to report all newly presenting patients with acute fovea-involving SMH secondary to nAMD of at least 2 disc diameters (DD) in greatest linear diameter. A follow up questionnaire was sent 6 months after initial presentation. Cases related to other causes were excluded.

**Results:** Twenty-nine cases were reported giving an incidence of 5.4 per million per annum but with a wide range across regions of 2-15. . The mean age was 83 years (range 66-96) and females accounted for 17/29 (59%). 15/29 (52%) had a past history of AMD, of which 7 was nAMD. 19/29 (66%) presented within 7 days of onset and the majority had SMH of less than 11 disc diameters (20/29,69%). Treatment options comprised: observation (n=6, 21%), anti-VEGF alone (n=6, 21%) or vitrectomy with co-application of tPA, anti-VEGF and gas (n=17, 58%). The vitrectomy group experienced the greatest change in vision from logMAR 1.89 to 1.50. (p=) Four out of 20 (20%) cases with 6 months follow up suffered a re-bleed at a mean time of 96 days. The incidence of submacular haemorrhage was calculated at 5.4 per million per year.

**Conclusion:** The incidence, clinical features and course of a consecutive national cohort of patients with SMH secondary to nAMD are presented.

## INTRODUCTION

The prognosis for neovascular age-related macular degeneration (nAMD) has been transformed by the use of intravitreal anti-vascular endothelial growth factor (anti-VEGF) drugs. Some patients, however, still have poor outcomes. One cause of severe visual loss in nAMD is submacular haemorrhage (SMH). This is relatively uncommon, but has a very poor prognosis untreated. {{503 Scupola,A. 1999;}} (25)

The optimum treatment of wet AMD complicated by significant SMH is uncertain. To date, several studies have suggested that treatment with anti-VEGFs alone may be superior to observation whilst others have suggested that displacement of blood with gas and sub-retinal or intravitreal tPA and anti-VEGF may be more optimal., Identifying the incidence of this complication and its optimal treatment has obvious implications for public health and cost effectiveness. (1-7)

The best evidence to determine if these more invasive procedures really represent an advance over management with intravitreal anti-VEGF alone would be a randomised clinical trial (RCT). To assist the design of such a trial, data on the incidence, natural history and outcome of patients presenting with SMH in the era of anti-VEGF treatment is needed. We therefore designed a national prospective observational study in Scotland, UK. Specifically, we aimed to assess the incidence of SMH occurring secondary to nAMD, the clinical features at presentation, the treatment modalities currently being used and finally prognostic factors which could help in future decision making.

## METHODS

This was a population-based, prospective observational study with active surveillance of cases through the Scottish Ophthalmological Surveillance Unit (SOSU) monthly reporting card scheme. SOSU has the same methodology as its sister organisation, the British Ophthalmological Surveillance Unit (BOSU) where several studies have been conducted previously. (8-12) Both were established to assist in the investigation of the incidence and clinical features of rare eye conditions of scientific and public health importance. The BOSU steering committee review all protocols of individual studies in order that certain basic criteria are met and to provide advice on the design of their questionnaires and studies. (13)

The SOSU surveillance scheme involves all consultant or associate specialist ophthalmologists with clinical autonomy in Scotland who form the reporting base. Ophthalmologists were asked to notify the study investigators, through the SOSU of all newly diagnosed cases of fovea-involving SMH of size greater than 2-disc diameter (DD). Case notifications were requested over the 12-month study period September 2013 to September 2014. All SMH not related to AMD were excluded.

Following case notification to the SOSU, every consultant ophthalmologist in Scotland was sent a detailed questionnaire by the study investigators requesting data on: visual acuity, lens status, fellow eye status, duration of symptoms (recorded as 1-7, 8-14, >14 days), previous treatment for SMH, size

of haemorrhage (recorded in groups 1-6, 7-11, 12-16 and >16 disc diameters (DD)), past history of nAMD, ocular co-morbidities, time to treatment and initial management. Outcome data were obtained from follow-up questionnaires sent to the reporting ophthalmologists 6 months after diagnosis. Follow-up data collected comprised: subsequent treatment, follow-up visual acuity, complications (re-bleed) and sight impairment registration details eligibility (partial/ severe). Ophthalmologists who did not return questionnaires were sent repeat request letters at 2 and 3 months after the initial request had been sent. The response rate was calculated as the number of questionnaires received over the total reporting cards received. (13)

Statistical analysis was performed with presentation of mean or median and range as appropriate. Visual acuity was converted to logMAR for analysis and paired t tests used to compare vision pre and post intervention. A p value of less than 0.05 was considered significant and a general linear model for significance.

#### *Incidence rate*

Scotland has been recognised in previous studies as a well-defined region with stable population demographics. (10,14) The proportion of the Scottish population of retirement age (65 years) has been shown to be relatively stable and representative of the whole UK population (18.0% vs 17.7%, respectively) and as such the Scottish population can be used as a focus population in a similar manner to previous studies. (10,15) . The male to female ratio is 49%:51%. The incidence rate was calculated as the number of reported cases as a proportion of the total population over the 1-year study period. The number of cases were also tracked to the source NHS trust in order to calculate the incidence per specific region of Scotland.

## **RESULTS**

Over the 12-month period between September 2013 and September 2014, a total of 29 yellow cards with reported cases (29 eyes) were returned and 29 initial questionnaires received giving a response rate of 100%. Six month follow up data was received on 20 of the 29 cases. The total Scottish population in 2013 was 5,327,700 giving an overall incidence of 5.4 per million per annum. The incidence varied by region from 15 per million in the Greater Glasgow and Clyde region (17 cases with a population of 1,137,000) to 2 per million in the Grampian region (1 case with a population of 526,000).

<b>TRUST OF REPORTED CASES</b>	<b>POPULATION</b>	<b>CASES</b>	<b>INCIDENCE</b>
NHS GREATER GLASGOW AND CLYDE	1,137,000	17	15.0
NHS AYRSHIRE AND ARRAN	400,000	3	7.5
NHS TAYSIDE	415,000	2	4.8
NHS LOTHIAN	800,000	3	3.8
NHS FORTH VALLEY	281,000	1	3.6

NHS HIGHLAND	320,000	1	3.1
NHS FIFE	359,000	1	2.8
NHS GRAMPIAN	526,000	1	1.9

Table 1 Reported cases and incidence per regional Scottish NHS trusts

Baseline data is presented in Table 1. The mean age was 83 years with 17 (59%) females. Fifteen (52%) had a past history of AMD of which 7 was nAMD. A total of 19/29 (66%) presented within 1-7 days of onset of symptoms. 7/29 (24%) presented greater than 2 weeks after onset of symptoms. Eleven (38%) had a SMH of size 7-11 DD while a further 9/29 (31%) were of size 2-6 DD.

Table 2 Clinical features at baseline

Age, years(mean, range)	83, 66-96
Sex n (%)	
Female	59%
Male	
Visual acuity, logMAR (mean, range)	1.85, 0.8-2.3
Fellow eye visual acuity	0.94, 0.2-2.3
Duration of symptoms, Days n(%)	
1-7	19 (66%)
8-13	3 (10%)
>14	7 (24%)
Size of SMH, DD n(%)	
2-6	9 (31%)
7-11	11 (38%)
12-16	3 (10%)
>16	6 (21%)
Known ocular co-morbidity of affected eye n(%)	
None	13 (45%)
Dry AMD	8 (28%)
nAMD	7 (24%)
OHT	1 (3%)
Lens status n(%)	
Phakic	69%
Pseudophakic	
Initial treatment n (%)	
Observation	6 (21%)
IVT aflibercept	1 (3%)
IVT ranibizumab	5 (17%)

PPV/ SRET tPA/ SRET ranibizumab/ GAS	17 (58%)
Time to treatment (days) Mean (range)	
Anti-VEGF	38 (6-55)
Vitrectomy	3 (0-6)
Overall	10 (0-55)

[VA - Visual acuity, SMH – submacular haemorrhage, DD – disc diameter, AMD 0 age related macular degeneration, nAMD – neovascular age related macular degeneration, PPV - Pars Plana Vitrectomy, IVT - Intravitreal, SRET - sub retinal). N=29 for all values.

### *Treatment modalities*

There were 3 management strategies observed: observation, anti-VEGF agents alone (either ranibizumab or aflibercept) and vitrectomy and co-application of intra-vitreous or subretinal tPA/anti-VEGF (see Table 1). No cases with expansile gas and intravitreal tPA/ Anti-VEGF were reported either as initial treatment or subsequently.

Table 3 **Follow-up data.**

Subsequent treatment n (%)	
None	7 (35%)
IVT ranibizumab	13 (65%)
Final visual acuity (mean, range)	1.61, 0-3
Final visual acuity fellow eye (mean, range)	0.91, 0-2.3
Re-bleed n (%)	4 (20%)
Sight impairment registration n (%)	
None	10 (50%)
Sight impairment	5 (25%)
Severe sight impairment	3 (15%)
Not known	2 (10%)

VA - visual acuity, IVT – intravitreal). N=20 for all values.

### *Visual acuity*

Overall the mean visual acuity non-significantly improved from 1.85 at baseline to 1.61 ( $p=0.072$ ) with differences, again non-significant between the groups, but with the greatest effect seen in the vitrectomy group. Eligibility for treatment in the UK NHS is dependent on being better than the UK NICE visual acuity cut off of 25 ETDRS letters (1.2 logMAR) or better. Of the 29 cases, 6 (20.7%) met these criteria. This percentage rose to 35.0% (7/20) at follow-up. Subsequent treatment was given in 13/20 (65.0%) of cases, all receiving intravitreal ranibizumab. The mean number of injections given was 2 (range 1-6).

	n	Baseline VA			Final VA			Change in VA	p value
		VA	SD	Range	VA	SD	Range		
Observation	6	1.83	0.55	1.04 - 2.30	1.81	0.82	1.14 - 3.00	-0.02	0.48
Anti-VEGF alone	6	1.72	0.57	1.00 - 2.30	1.77	0.68	1.00 - 2.30	0.05	0.45
Vitrectomy	17	1.89	0.49	0.8 - 2.30	1.5	0.79	0 - 2.30	-0.39	0.35

Table 4 Changes in visual acuity across the three management groups. (VA - visual acuity, SD - standard deviation, VEGF - Vascular endothelial growth factor)

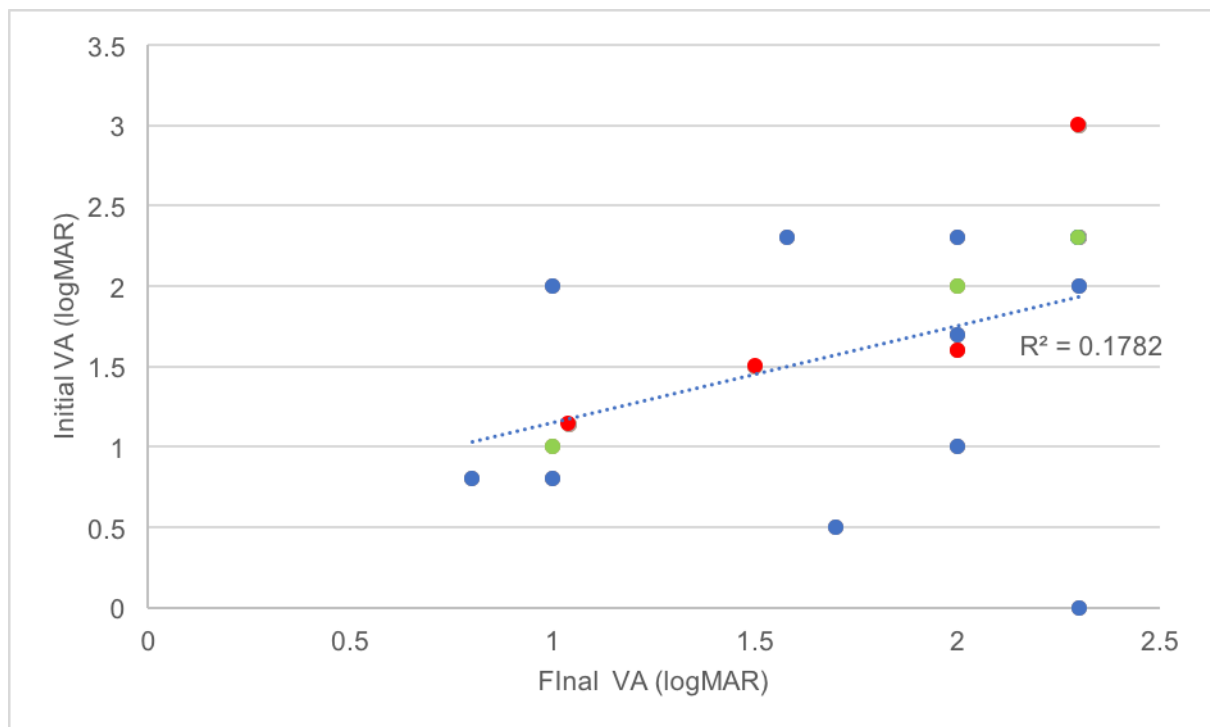


Figure 1 Initial and final logMAR visual acuity across reported management groups (Observation – green, Anti-VEGF alone – red, vitrectomy – blue). The line represents Pearson’s line of correlation of the whole cohort.

#### Duration of symptoms

Those presenting within the median of 1- 7 days of onset of symptoms showed a mean improvement in visual acuity from 1.76 to 1.37 (-0.39). Conversely, those presenting greater 7 days had a decline in visual acuity at follow-up from 1.78 to 1.87 (0.09). Overall, the duration of symptoms was not a significant predictor of final visual acuity ( $p=0.381$ )

#### Size of haemorrhage

The median size of SMH was 7-11 DD. There was no significant differences in baseline and follow up between any of the groups but the greatest improvement was seen in the smallest SMH size group of

2-6DD (p=0.251) In contrast, a decline in mean visual acuity was seen in haemorrhages of greater than 16 DD (see Table 4)

Size of SMH (DD)	n	Baseline VA			Final VA			Change in VA	p value
		VA	SD	Range	VA	SD	Range		
2 - 6	9	1.51	0.48	1.04 - 2.00	1.21	0.26	1.14 - 1.5	-0.3	0.2
7 - 11	11	1.8	0.6	0.8 - 2.30	1.73	0.89	0.50 - 3.00	-0.07	0.42
12 - 16	3	2.2	0.17	2.00 - 2.30	2.15	0.21	2.00 - 2.30	-0.05	0.39
> 16	6	1.74	0.6	1.00 - 2.30	1.78	0.56	0.8 - 2.30	0.04	0.33

Table 5 Changes in visual acuity with different size of Submacular haemorrhage. VA – visual acuity, SD – standard deviation, DD – disc diametres

### *Complications*

4/20 (20%) suffered re-bleeds with a mean time of 96 days (range 52-170) from the date of treatment. One case was in the observation group while the other 3 were in the surgical group. The mean visual acuity in this group improved from 1.95 to 1.77 despite the rebleed. Three out the 4 (75%) were treated with subsequent anti-VEGF. At 6-month follow-up, 8/20 (40%) were eligible for sight impairment registration and 3 (15%) registered as severely sight impaired.

## DISCUSSION

In this study, we presented data from a national surveillance study into all cases of acute submacular haemorrhage over a 12-month period in Scotland. Through this prospective study, we have identified the incidence rate of fovea-involving submacular haemorrhage of 5.4 per million per year. It was noted on postcode data that the incidence varied greatly by region ranging from 15 per million to 2 per million. There are a number of reasons for these variations. The first may be a degree of under-reporting which is evident in any surveillance scheme, although the response rate from participating ophthalmologists in the BOSU scheme has been consistently more than 70%. (13) Secondly, patients may fail to present due to access to healthcare. For example, NHS Highland covers an estimated area of 12,500 square miles and serves a population of 320,000. In contrast to this, NHS Greater Glasgow and Clyde has a population of 1,137,000 and 17 reported cases (incident rate of 15 per million per year). With an area of 452 square miles, it's important to know that its population density is much higher than NHS Highland at 2,515 people per square mile (compared to just 26 people per square mile). This might have contributed to the variations in reporting rates. One can also suppose that these differences across regions are genuine, however this was not seen in a pilot study which showed comparable incidence rates between Sunderland and Glasgow (24 per million per year) although these are very comparable areas in terms of population density, healthcare provision and deprivation indices. (7) A smaller size haemorrhage (<7 DD) was associated with a better visual prognosis. Conversely, massive submacular haemorrhages (>16 DD) were associated with a poorer visual prognosis as found by previous studies. (7)

In our study, those that were observed showed a slight decline in visual acuity whilst those who were treated surgically showed some, albeit non-significant improvement in visual acuity. Surgical intervention was exclusively with pars plana vitrectomy and co-application of tPA/anti-VEGF with gas exchange. This intervention has been associated with complete displacement of the submacular haemorrhage and improvement in post-operative visual acuity. (5) Furthermore, the surgical intervention in this case led to an increase in the percentage of patients (18% to 42%) who were eligible for intravitreal anti-VEGF as based on the UK vision criteria which may justify its use in cases where no alternative therapy is indicated. Patients treated with anti-VEGF agents alone resulted in maintained and in certain cases, improved visual outcomes compared to the natural history of the submacular haemorrhage which concurs with previous reports. (1-2,17-19, 24-25) It is interesting however to note that those who were treated with anti-VEGF alone waited a mean number of 38 days while those who were treated surgically waited a mean number of 3 days. Whilst it is known that prompt surgical treatment improves outcomes, the relationship between treatment time and outcome with anti-VEGF alone is unclear but the anti-VEGF trials showed duration of symptoms prior to treatment was related to outcome so it can be concluded that prompt treatment, even with anti-VEGF alone can help prevent severe visual loss. (1-2,17-19) The pressures of service delivery, especially in the National Health Service, mean that it is often days or weeks until patients are seen, have the appropriate diagnostic investigations, a management plan is arranged and executed. Strategies to



highlight time sensitive conditions such as SMH must be in place if severe visual loss is to be prevented.

It is interesting to note that there were no reported cases of the use of pneumatic displacement with intravitreal tPA although this has been widely reported as an effective strategy combined with anti VEGFs previously.(17-21). Having said this, the relative efficacy of expansile gas and intravitreal TPA compared to vitrectomy with subretinal TPA and air or gas is uncertain. A recent RCT showed no difference in results between the two modalities but previous studies have shown a higher efficacy of subretinal TPA over intravitreal TPA in terms of displacement of blood eccentrically to fovea. (22-23) A study of vitrectomy combined with subretinal TPA and air reported 3 cases that were successfully displaced that had previously failed to displace with expansile gas and intravitreal TPA and the vitrectomy technique may offer advantages in patients unable to posture. (4) It appears that in Scotland displacement with the expansile is not popular which may be due to a variety of possible reasons including personal surgical preference, patient choice and the lack of ability, or perceived risks of posturing in the age group affected. (21)

The evidence base for the treatment of SMH associated with AMD largely comprises case-series which tend to focus on surgeon-selected cases and a variety of criteria to guide individual treatment choices. Therapeutic decision-making is difficult due to a lack of standardisation in both the classification of SMH and outcome reporting. (16) The strength of this study is that we report on the presentation and management of all cases over a one-year period with 6-month follow data to give a true picture of the cases seen in clinical practice and real world outcomes from a range of management options and which we hope will help guide the design of a future RCT. There are however several limitations to the study, including the lack of access to fundal imaging to ascertain the precise features of the haemorrhages and absence of protocol refracted visual acuities. Follow up was also limited to 6 months and incomplete.

In conclusion, this prospective national surveillance study has identified an incidence for submacular haemorrhage of 5.4 per million per year but with a wide range of 2-15. In addition, we highlight the benefit of prompt surgical intervention in the quest to improve vision. It is hoped that this surveillance study will inform future randomised control studies. In particular, further studies are indicated to clearly define the role of surgical intervention as compared to anti VEGF treatment alone in the treatment of fovea-involving submacular haemorrhage.

## **ACKNOWLEDGEMENTS**

The authors are very grateful for the opportunity to perform this project in conjunction with the Scottish Ophthalmic Surveillance Unit and wish to thank Mr Barny Foot for his valuable advice. The authors also acknowledge the contribution of the ophthalmologists throughout Scotland who made this study possible by reporting cases to the SOSU and providing the necessary information about the patients.

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