

VISION ACADEMY VIEWPOINT

The Vision Academy is a partnership between Bayer and ophthalmic specialists, established with the aim of addressing key clinical challenges in the field of retinal diseases: www.visionacademy.org.

Management of Subfoveal Hemorrhage

Background

Subretinal hemorrhage is a manifestation of neovascular age-related macular degeneration (nAMD) in which blood from the retinal or choroidal circulation accumulates between the retinal pigment epithelium (RPE) and the neurosensory retina, causing severe visual impairment when the fovea is involved.¹

Currently, there is a lack of evidence-based research and rigorous guidelines for the management of patients with subfoveal hemorrhage secondary to nAMD. In the past decade, a number of reports have demonstrated positive outcomes with a range of different treatments, including intravitreal anti-vascular endothelial growth factor (anti-VEGF), pneumatic displacement (PD), vitrectomy, intravitreal or subretinal tissue plasminogen activator (tPA), and various combinations thereof. Despite these, there remains a lack of consensus among vitreoretinal specialists on the optimal approach to managing patients with subfoveal hemorrhage.

This Viewpoint offers pragmatic clinical considerations and expert recommendations on defining, imaging, and treating subfoveal hemorrhage in nAMD.

Endorsed by the Vision Academy in
July 2023.

Date of review: July 2025



Full consensus



Variations in opinion

Viewpoint

1. Definition

There is currently a lack of guidance on determining treatment of subfoveal hemorrhage based on size and thickness. Subretinal hemorrhages are often classified by size as follows:



- Small – measuring at least 1 disc diameter (DD) but smaller than 4 DDs¹
- Medium – measuring at least 4 DDs but does not extend beyond the temporal vascular arcades¹
- Large – extends beyond the temporal vascular arcades but not past the equator²
- Massive – extends past the equator in at least two quadrants^{2,3}

'Thick' subfoveal hemorrhages (usually measuring >500 µm in thickness) are defined as blood under the fovea causing obvious elevation of the retina with obscuration of the RPE on fundus examination.^{1,4} While many clinicians advocate the treatment of extrafoveal or 'thin' subfoveal hemorrhages with anti-VEGF monotherapy,⁵ several studies have demonstrated poor visual outcomes with larger or thicker subfoveal hemorrhages.^{3,6} However, these are becoming increasingly uncommon in clinical practice because of improved access to treatments at an earlier stage of hemorrhage manifestation.

2. Imaging

Color fundus photography, fundus autofluorescence, and spectral domain optical coherence tomography (OCT), including use of the enhanced-depth imaging mode, are important tools for localizing hemorrhage within the retinal layers to distinguish between subretinal and sub-RPE blood, and for objectively quantifying hemorrhage size.¹ While fluorescein angiography may be limited by the masking effect of subretinal blood, indocyanine green angiography (ICGA) may be a more useful method for hemorrhage visualization.¹ This may be especially true in populations where polypoidal choroidal vasculopathy (PCV) is highly prevalent because the infrared light employed in ICGA has a high penetration through RPE and blood.¹



The Vision Academy recommends multimodal imaging with OCT to determine several prognostic factors for subfoveal hemorrhage, including hemorrhage size, thickness, and etiology, in order to drive treatment choice.^{2,6-8}

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Always refer to local treatment guidelines and relevant prescribing information.

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References

1. Stanescu-Segall D, Balta F and Jackson TL. Submacular hemorrhage in neovascular age-related macular degeneration: a synthesis of the literature. *Surv Ophthalmol* 2016; 61 (1): 18–32.
2. Yiu G and Mahmoud TH. Subretinal hemorrhage. *Dev Ophthalmol* 2014; 54: 213–222.
3. Fine HF, Iranmanesh R, Del Priore LV *et al*. Surgical outcomes after massive subretinal hemorrhage secondary to age-related macular degeneration. *Retina* 2010; 30 (10): 1588–1594.
4. Chang W, Garg SJ, Maturi R *et al*. Management of thick submacular hemorrhage with subretinal tissue plasminogen activator and pneumatic displacement for age-related macular degeneration. *Am J Ophthalmol* 2014; 157 (6): 1250–1257.
5. Steel DHW and Sandhu SS. Submacular haemorrhages associated with neovascular age-related macular degeneration. *Br J Ophthalmol* 2011; 95 (8): 1051–1057.
6. Scupola A, Coscas G, Soubbrane G *et al*. Natural history of macular subretinal hemorrhage in age-related macular degeneration. *Ophthalmologica* 1999; 213 (2): 97–102.
7. Karagiannis D, Chatziralli I, Kaprinis K *et al*. Location of submacular hemorrhage as a predictor of visual outcome after intravitreal ranibizumab for age-related macular degeneration. *Clin Interv Aging* 2017; 12: 1829–1833.
8. Lin T-C, Hwang D-K, Lee F-L *et al*. Visual prognosis of massive submacular hemorrhage in polypoidal choroidal vasculopathy with or without combination treatment. *J Chin Med Assoc* 2016; 79 (3): 159–165.
9. Shin K-H, Lee TG, Kim JH *et al*. The efficacy of intravitreal aflibercept in submacular hemorrhage secondary to wet age-related macular degeneration. *Korean J Ophthalmol* 2016; 30 (5): 369–376.
10. Kim KH, Kim JH, Chang YS *et al*. Clinical outcomes of eyes with submacular hemorrhage secondary to age-related macular degeneration treated with anti-vascular endothelial growth factor. *Korean J Ophthalmol* 2015; 29 (5): 315–324.
11. Liu EM, Rajagopal R, Smith BT *et al*. Management of large submacular hemorrhages due to exudative AMD utilizing pars plana vitrectomy, subretinal tissue plasminogen activator, and gas insertion compared with anti-vascular endothelial growth factor alone. *J Vitreoretin Dis* 2017; 1: 34–40.
12. Cho HJ, Koh KM, Kim JH *et al*. Intravitreal ranibizumab injections with and without pneumatic displacement for treating submacular hemorrhage secondary to neovascular age-related macular degeneration. *Retina* 2015; 35 (2): 205–212.
13. de Silva SR and Bindra MS. Early treatment of acute submacular hemorrhage secondary to wet AMD using intravitreal tissue plasminogen activator, C₃F₆, and an anti-VEGF agent. *Eye (Lond)* 2016; 30 (7): 952–957.
14. González-López JJ, McGowan G, Chapman E *et al*. Vitrectomy with subretinal tissue plasminogen activator and ranibizumab for submacular haemorrhages secondary to age-related macular degeneration: retrospective case series of 45 consecutive cases. *Eye (Lond)* 2016; 30 (7): 929–935.
15. Treumer F, Wienand S, Purtskhvanidze K *et al*. The role of pigment epithelial detachment in AMD with submacular hemorrhage treated with vitrectomy and subretinal co-application of tPA and anti-VEGF. *Graefes Arch Clin Exp Ophthalmol* 2017; 255 (6): 1115–1123.
16. Karamitsos A, Papastavrou V, Ivanova T *et al*. Management of acute submacular hemorrhage using intravitreal injection of tissue plasminogen activator and gas: a case series. *SAGE Open Med Case Rep* 2020; 8: 2050313X20970337.
17. Fassbender JM, Sherman MP, Barr CC *et al*. Tissue plasminogen activator for subfoveal hemorrhage due to age-related macular degeneration: comparison of 3 treatment modalities. *Retina* 2016; 36 (10): 1860–1865.
18. Klettner A, Grottelüschen S, Treumer F *et al*. Compatibility of recombinant tissue plasminogen activator (rtPA) and aflibercept or ranibizumab coapplied for neovascular age-related macular degeneration with submacular haemorrhage. *Br J Ophthalmol* 2015; 99 (6): 864–869.
19. Klettner A, Puls S, Treumer F *et al*. Compatibility of recombinant tissue plasminogen activator and bevacizumab co-applied for neovascular age-related macular degeneration with submacular hemorrhage. *Arch Ophthalmol* 2012; 130 (7): 875–881.
20. Dumitrescu-Dragan A and Elgohary M. Outcome of submacular haemorrhage (SMH) displacement and drainage following injection of intravitreal tissue plasminogen activator (tPA). Poster presented at the 15th Annual Meeting of the European VitreoRetinal Society, Venice, Italy, September 12–14, 2015.
21. Gabrielle P-H, Delyfer M-N, 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. In press. doi: 10.1016/j.ophtha.2023.04.014.
22. Jackson TL, Bunce C, Desai R *et al*. Vitrectomy, subretinal Tissue plasminogen activator and Intravitreal Gas for submacular haemorrhage secondary to Exudative Age-Related macular degeneration (TIGER): study protocol for a phase 3, pan-European, two-group, non-commercial, active-control, observer-masked, superiority, randomised controlled surgical trial. *Trials* 2022; 23 (1): 99.

3. Treatment

Based on an extensive literature search, the Vision Academy makes the following recommendations for the treatment of subfoveal hemorrhage in nAMD.

To minimize the risk of irreversible retinal damage, the Vision Academy recommends prompt initiation of anti-VEGF as a first-line treatment for subfoveal hemorrhage in nAMD, as well as in cases of PCV, in patients who are able to attend regular follow-up appointments. Careful monitoring with continued anti-VEGF treatment is important to minimize the risk of breakthrough hemorrhage and other complications. Further studies and large-scale randomized controlled trials are warranted to determine the full effects of hemorrhage duration on clinical outcomes with anti-VEGF therapy.



Most reports on anti-VEGF treatment of subfoveal hemorrhage in nAMD to date have come from non-randomized comparative studies or small, retrospective, uncontrolled case series reporting positive visual outcomes with anti-VEGF as monotherapy⁹⁻¹¹ and in combination with tPA, PD, and/or surgery.¹²⁻¹⁶ Significant visual improvements seen in eyes with good baseline vision and short hemorrhage duration demonstrate the importance of early initiation of anti-VEGF treatment⁹; however, small sample sizes and differences in baseline features, inclusion criteria, and treatment regimens make it difficult to compare existing studies on anti-VEGF therapy.

The Vision Academy recommends intravitreal tPA with PD for medium, large, or thick subfoveal hemorrhages in patients with poor baseline vision (<20/200), at the discretion of the physician.



Evidence has demonstrated favorable visual outcomes with intravitreal tPA in combination with PD (both with and without vitrectomy) compared with PD alone for the treatment of subretinal hemorrhage.¹⁷ While a sub-RPE hemorrhage in association with a subretinal hemorrhage involving the fovea does not preclude the use of PD or vitrectomy, the location and size of the sub-RPE component may affect the decision to perform these procedures.

The Vision Academy recommends surgical intervention only for severe subretinal hemorrhages, as determined by thickness and location. In all other cases, prompt anti-VEGF treatment and careful monitoring are recommended.



Evidence suggests that pars plana vitrectomy (PPV) in combination with subretinal tPA and PD may offer a more effective option than anti-VEGF monotherapy for the treatment of patients with thick or large hemorrhages and poor baseline vision.^{4,11} However, without adequate prospective studies, it is not possible to draw comparisons between surgery and other treatment modalities because of likely variation in surgical techniques between reports.

Further considerations

One *in vitro* study assessed the anti-angiogenic activities of anti-VEGF agents when co-applied with tPA or plasmin, an enzyme that is liberated from the blood by tPA; when co-applied with plasmin at a concentration lower than the clinical dose, aflibercept was cleaved and its VEGF-binding ability reduced.¹⁸ Inhibition of anti-angiogenic activity was not observed *in vitro* with aflibercept, ranibizumab, or bevacizumab when co-applied at clinical concentrations with plasmin,^{18,19} nor with any of the three anti-VEGF molecules in a small retrospective case series of patients with submacular hemorrhage due to nAMD.²⁰ The STAR study (NCT02557451), a French multi-center randomized trial in 90 patients, demonstrated that PPV combined with tPA and anti-VEGF was not superior to PD combined with anti-VEGF therapy.²¹ The TIGER study (NCT04663750), a Phase III, pan-European, observer-masked, superiority, randomized controlled trial, is assessing the efficacy of anti-VEGF therapy alone versus with PPV in combination with subretinal tPA (n=210), and will provide valuable data to help support clinical decision-making.²²



Regional variations in treatment reimbursement policies may affect treatment decisions. While economic factors often play a big role in determining treatment, the decision to perform surgery should be based primarily on clinical experience and consideration of the available evidence.

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