Review of current management of submacular hemorrhage

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Purpose of review
Subretinal hemorrhage (SRH) is most commonly associated with neovascular age-related macular degeneration (nAMD) and can cause profound vision loss in the macula through mechanical, toxic, and inflammatory mechanisms. Submacular hemorrhage (SMH) lacks consensus on management. This review summarizes current treatment options, key comparative studies, and ongoing challenges, with emphasis on SMH management.

Recent findings
Antivascular endothelial growth factor (anti-VEGF) therapy remains central to SMH management, with outcomes comparable to surgery in small to moderate hemorrhages. Pneumatic displacement (PD) with or without recombinant tissue plasminogen activator (rtPA) shows the greatest comparative benefit in more extensive SMH. Adjunctive rtPA improves hemorrhage displacement rates, and meta-analyses support its efficacy with anti-VEGF therapy. Pars plana vitrectomy (PPV) remains an option for large or refractory hemorrhages but has not consistently shown superior visual outcomes compared to less invasive modalities.

Summary
Early intervention is consistently associated with improved outcomes, but there is no universally accepted treatment algorithm. Ongoing randomized trials and advances in multimodal imaging have the potential to refine patient selection and treatment strategies. Future efforts should focus on balancing efficacy, safety, and cost-effectiveness to establish evidence-based guidelines for SMH management.

Keywords
antivascular endothelial growth factor, pars plana vitrectomy, recombinant tissue plasminogen activator, submacular hemorrhage, subretinal hemorrhage

INTRODUCTION

Subretinal hemorrhage (SRH) is the accumulation of blood between the neurosensory retina and retinal pigment epithelium (RPE). SRH, particularly when it involves the macula (submacular hemorrhage, SMH), carries significant visual morbidity through a variety of mechanisms, including direct mechanical distortion, photoreceptor toxicity from iron accumulation, and reactive inflammatory responses [1]. SMH can result from a variety of causes, with neovascular age-related macular degeneration (nAMD) and polypoidal choroidal neovascularization (PCV) being the most common [2]. Other etiologies include trauma, myopic choroidal neovascularization (CNV), and ruptured retinal artery macroaneurysms (RAM) [2]. This review focuses on SMH management secondary to nAMD and PCV.

While the exact incidence is uncertain, data from the *Fight Retinal Blindness!* registry reported SMH incidence as 4.6 per 1000 treated nAMD eyes per year [3]. Notably, PCV is reported to have a higher incidence and larger size of SMH. The risk factors associated with SMH are not well defined; however, several studies provide some insight [4]. Gabrielle *et al.* identify eyes with disciform scar CNV at baseline as a potential risk factor for SMH development in nAMD-treated eyes, while the type of antivascular endothelial growth factor (VEGF) and injection interval had no influence [3]. In a nationwide analysis of over 140,000 eyes with SMH associated with nAMD, Kaufmann *et al.* found anticoagulant and antiplatelet use to have increased odds of SMH

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KEY POINTS

- Subretinal hemorrhage, most often linked to neovascular age-related macular degeneration, causes severe vision loss through mechanical, toxic, and inflammatory damage.
- Antivascular endothelial growth factor therapy remains the cornerstone of treatment, showing comparable outcomes to surgery in small-to-moderate hemorrhages.
- Pneumatic displacement and recombinant tissue plasminogen activator offer added benefit in larger or more complex submacular hemorrhages.
- Pars plana vitrectomy remains reserved for extensive or refractory cases, with visual outcomes similar to less invasive options but higher procedural risk.
- Early intervention and individualized treatment planning are key, with ongoing trials like TIGER expected to guide future standardized management algorithms.

development (odds ratio 1.46, 1.38, respectively), though overall findings remain inconsistent [5▪].

Left untreated, SMH can result in higher rates of subretinal fibrosis, visual acuity (VA) decline, and macular atrophy [3,6–8]. Treatment options include anti-VEGF monotherapy to prevent further hemorrhage or approaches aimed at hemorrhage displacement to mitigate iron toxicity and limit photoreceptor injury [9]. Although many combinations of in-office and operative pharmacological, pneumatic, and surgical methods are available, there is limited consensus on modality and patient selection [10▪,11,12]. This review provides an overview of current SMH management, examining the efficacy and safety of current approaches, comparative outcomes between modalities, and ongoing controversies.

Mechanisms and pathophysiology

Vision loss in SMH arises from three main interacting mechanisms [2]. The formation of a physical barrier between photoreceptors and the RPE limits the diffusion of nutrients and oxygen into the cells, leading to cell death [1]. Concurrently, heme degradation leads to iron-mediated oxidative damage and apoptosis of the photoreceptor layer and RPE cells [13]. This effect is quick and can begin within hours of hemorrhage onset [13,14]. Additionally, mechanical traction from the clot can cause photoreceptors to physically pull away from the RPE, leading to permanent retinal damage and a fibrotic disciform scar [1,15]. These mechanisms guide the rationale behind treatment approaches aimed at early and effective displacement of the hemorrhage [11].

Current therapeutic options and advances

Recent evidence continues to refine the management of SMH. However, consensus on the optimal treatment strategy remains elusive, as clinicians weigh efficacy, safety, and invasiveness across available therapeutic options. Current approaches can be categorized into the following major categories: anti-VEGF monotherapy, pneumatic displacement, and pars plana vitrectomy (PPV). Recombinant tissue plasminogen activator (rtPA) facilitates clot breakdown and can be administered either intravitreally or subretinally in combination with pneumatic displacement or PPV, respectively. In practice, anti-VEGF therapy is frequently combined with the displacement approaches.

Antivascular endothelial growth factor monotherapy

Anti-VEGF monotherapy continues to be a widely utilized option in the management of SMH secondary to nAMD, with representative studies summarized in Table 1. A 2025 meta-analysis of 43 observational studies reported that anti-VEGF monotherapy achieved similar VA gains as compared to surgical intervention [16▪]. Notably, anti-VEGF therapy demonstrated a more favorable safety profile, including lower rates of retinal detachment (RD) (0.1% vs. 10.6%), cataract formation (0% vs. 4.6%), and proliferative vitreoretinopathy (PVR) (0.1% vs. 2.0%) [16▪]. Despite inherent selection bias between the two groups, these findings support anti-VEGF monotherapy as an effective, low-risk option, particularly in small to moderate SMH or in poor surgical candidates.

In larger SMH's [>3 disc diameters (DD)], a recent study of 31 eyes compared outcomes of anti-VEGF monotherapy to vitrectomy and found no significant differences in 12-month best corrected visual acuity (BCVA) between the two groups, with neither group demonstrating meaningful improvement from baseline [17]. Instead, only lens status, central foveal thickness, and baseline VA were shown to be predictors of better VA outcome [17]. This reflects that clot burden of larger hemorrhages may limit the effectiveness of any treatment modality. Conversely, a multicenter real-world cohort of 66 eyes with a mean SMH size of 3.64 DD found that although 12-month VA did not differ between anti-VEGF monotherapy and surgical displacement, the surgical group achieved a greater adjusted 12-month VA gain despite more severe baseline hemorrhage, supporting consideration for surgery for larger SMH [18].

Table 1. Summary of anti-VEGF monotherapy studies

Author	Year	Study design	Eyes (*n*)	SMH criteria, etiology	Treatment details	Follow-up (months)	Pretreatment BCVA, logMAR (mean ± SD)	Final BCVA, logMAR (mean ± SD)	Pretreatment BCVA (Snellen)	Final BCVA (Snellen)	Key findings
Maruyama-Inoue *et al.*	2023	Retrospective, single center	62	≥ 1 DA, treatment naïve nAMD	3 monthly loading injections of aflibercept or brolucizumab, then PRN or fixed	12	VH−: 0.42 ± 0.36 VH+: 0.45 ± 0.45	0.36 ± 0.48 0.92 ± 0.51	20/53 20/56	20/46 20/166	BCVA improved significantly in eyes without VH ($P = 0.040$); VH developed in 8.1% of eyes; larger DA and younger age associated with VH development
Miyazato *et al.*	2025	Retrospective, single center	31	> 3 DA fovea-involving, nAMD	Aflibercept or brolucizumab: 3-dose load, then PRN/proactive vs. PPV	12	MT: 0.56 ± 0.27 PPV: 1.04 ± 0.55	0.59 ± 0.52 1.09 ± 0.52	20/73 20/219	20/79 20/246	Final BCVA did not improve significantly from baseline ($P > 0.05$); lens status, CFT height, baseline VA associated with 12-month VA
Chirpaz *et al.*	2025	Retrospective, multicenter	66	≥ 1 DD, nAMD	Anti-VEGF per center protocol vs. PPV	12	MT: 0.74[a] PPV: 1.05[a]	0.57[a] 0.49[a]	20/110 20/224	20/74 20/62	12-month VA similar to PPV; Maximum SMH thickness associated with poorer 12-month VA; SMH recurrence more common in MT group, MH more common in PPV group, no significant difference between them
Shaheen *et al.*	2025	Systematic Review and Meta-Analysis	1415	AMD-related	Anti-VEGF agent MT vs. PPV	12	–	Δ logMAR MT: −0.16 (95% CI: −0.24, −0.08) PPV: −0.36 (95% CI: −0.68, −0.04)	–	–	Pooled VA outcomes similar to PPV; MT had more favorable safety profile, MT vs. PPV: PVR 0.1 vs. 2.0%; RD 0.1 vs. 10.6%; recurrent SMH 5.4 vs. 5.3%;

– Indicates item not reported or specified; BCVA, best-corrected visual acuity; CFT, central foveal thickness; DA, disc area; DD, disc diameter; MH, macular hole; MT, Anti-VEGF monotherapy; nAMD, neovascular age-related macular degeneration; PPV, pars plana vitrectomy; PRN, pro re nata; PVR, proliferative vitreoretinopathy; SMH, submacular hemorrhage; VH, vitreous hemorrhage.
[a]Reported in Snellen decimal acuities, converted to logMAR for consistency.

To date, no single anti-VEGF agent has demonstrated superiority in treating SMH. A 2023 retrospective study of 62 treatment-naïve SMH eyes treated with aflibercept or brolucizumab, found no significant 12-month VA difference between agents, with improvement mainly in eyes without breakthrough vitreous hemorrhage (VH) [19]. Overall, current data continue to support anti-VEGF monotherapy as an effective first-line strategy, particularly for smaller hemorrhages, though larger or refractory hemorrhages may warrant adjunctive displacement methods.

Pneumatic displacement

Pneumatic displacement (PD) uses intravitreal injection of expansile gas (SF_6 or C_3F_8) to displace blood from the fovea, with evidence from relevant published studies summarized in Table 2. PD offers a minimally invasive alternative to surgery and can be conducted with or without intravitreal rtPA and anti-VEGF therapy.

The benefits of combining PD with anti-VEGF therapy have been explored in several studies with mixed results. A retrospective study by Wakabayashi *et al.* of 47 eyes with PCV-associated large SMH (>2 DD) showed superior 12-month BCVA improvement in patients receiving intravitreal aflibercept and PD compared to patients receiving aflibercept alone (≥ 3-line gain in 60.0% vs. 18.2% of patients, respectively) [20▪]. Notably, SMHs of the combination group had a mean SMH thickness of 551 μm, suggesting the utility of PD in thicker hemorrhages specifically [20▪]. In contrast, Sim *et al.* found that while PD combined with anti-VEGF accelerated blood displacement in treatment naïve nAMD and PCV, final visual outcomes were comparable to anti-VEGF monotherapy at one year [21]. Comparing between anti-VEGF agents, a 2025 retrospective study by Chakraborty *et al.* found comparable BCVA improvement between innovator ranibizumab (1.15–0.51 logMAR) and its biosimilar (1.17–0.53 logMAR) and similar reductions in central macular thickness at 6 months when combined with PD [22]. Other studies have also explored factors that may predict a more favorable response to PD. In a 2025 analysis of 56 eyes, thinner residual hemorrhage at 1 week and treatment naïve status were described to be independent predictors of BCVA improvement at 3 months [23].

There continues to be ongoing debate on the utility of adjunctive rtPA in PD. A recent retrospective study of 127 eyes with SMH treated with PD and anti-VEGF, with or without intravitreal rtPA, found both groups achieving comparable VA gains and high rates of complete blood displacement (92.1% vs. 90.9%, respectively) at 12 months [24]. However, the non-rtPA group had a significantly higher incidence of breakthrough VH (OR 7.03, P = 0.004), specifically in SMH size >4 DD, suggesting the utility of adjunctive rtPA in reducing the risk of VH in more extensive SMH [24]. Similar visual improvement using PD without rtPA has also been reported in a smaller series by Ota *et al.*, where earlier treatment was associated with improved outcomes [25].

Further, the *TAPAS* study, a multicenter randomized clinical trial comparing four adjunctive strategies after baseline ranibizumab: sham (n=23), intravitreal C_3F_8 (n=11), intravitreal rtPA (n=11), and combined gas plus rtPA (n=11), showed that adjunctive intravitreal rtPA, but not C_3F_8 gas alone, produced significantly improved 3 month BCVA (+16 ETDRS letters; P=0.02) and faster hemorrhage clearance compared to eyes not receiving rtPA [26]. Together, this evidence supports the efficacy of adjunctive intravitreal rtPA in cases of SMH secondary to nAMD [27–29]. Additionally, long-term data showed sustained benefit of triple injection of rtPA, SF_6 gas, and bevacizumab, showing a mean +28-letter gain and improvement in central retinal thickness (CRT) maintained over a mean final follow-up of 4.4 years [28]. Notably, RPE tears developed in 13.5% of eyes (5/37) and the authors cite prior studies that link large PED height to increased RPE tear risk, although this was not evaluated in their cohort [28].

Pars plana vitrectomy

PPV remains an important therapeutic option for SMH, particularly for the management of large or refractory SMH, with reported surgical techniques and outcomes summarized in Table 3. However, its advantage over less-invasive approaches is not clearly established.

The multicenter *STAR* randomized controlled trial (RCT) analyzed 90 eyes with nAMD who developed SMH more than 2 DD and received intervention within 14 days. Treatment included two groups: those who had PPV, subretinal rtPA, and SF_6 tamponade vs. PD and intravitreal rtPA, with both groups receiving anti-VEGF therapy. Both the PPV and PD groups had improvement in BCVA at 3 months (16.8 letters vs. 16.4 letters, P=0.767) and 6 months (17.2 letters vs. 15.4 letters, P=0.776). This study supports prompt intervention and possibly the use of less invasive methods for treating SMH [30].

Chew *et al.* first defined the Manchester protocol as a stepwise approach starting with intravitreal rtPA and 0.3 ml 100% C_3F_8 gas injection with escalation to PPV, subretinal rtPA, and 20% SF_6 gas tamponade if displacement is inadequate in 72 h, and showed it can achieve successful anatomic displacement and

Table 2. Summary of pneumatic displacement studies

Author	Year	Study design	Eyes (*n*)	SMH criteria, etiology	Treatment details	Follow-up (months)	Pretreatment BCVA, logMAR (mean ± SD)	Final BCVA, logMAR (mean ± SD)	Pretreatment BCVA (Snellen)	Final BCVA (Snellen)	Key findings
Sim *et al.*	2024	Retrospective, single center	57	>2 mm^2, fovea-involving, treatment naïve nAMD or PCV	PD (SF_6 or C_3F_8) + aflibercept vs. aflibercept MT	12	PD: 1.3±0.6 Non-PD: 1.2±0.6	1.1±0.9 0.7±0.6	20/399 20/317	20/252 20/100	No significant difference in mean 12-month VA between PD and non-PD group (P= 0.09); faster resolution of SMH in PD group; RPE rip at 1-month in 2 PD eyes
Wakabayashi *et al.*	2025	Retrospective, single center	47	≥ 2 DD, PCV	PD (C_3F_8) + aflibercept vs. aflibercept alone	12	PD: 0.78±0.46 Non-PD: 0.83±0.66	0.26±0.42 0.85±0.57	20/120 20/135	20/36 20/142	PD + aflibercept achieved superior 12-month VA; 1 week displacement of SMH achieved in 21 eyes (84%) in PD + aflibercept vs. no eyes in MT (P=<0.001); macular fibrosis in 0 eyes in PD group vs. 35% in MT at 12-month
Watanabe *et al.*	2025	Retrospective, single center	56	nAMD	PD (SF_6)	3	0.86±0.52	0.54±0.45	20/145	20/69	Treatment naïve status, thinner 1 week SMH, and worse baseline VA were predictors of 3-month VA gain
Ota *et al.*	2025	Retrospective, single center	22	>2 DD, fovea-involving, nAMD	PD (SF_6) + aflibercept or ranibizumab	12	0.92±0.47	0.56±0.51	20/166	20/73	PD + anti-VEGF significantly improved VA over 12 months (P=0.01)
Chakraborty *et al.*	2025	Retrospective, single center	67	Treatment naïve nAMD	Innovator ranibizumab + C_3F_8 vs. biosimilar + C_3F_8	6	Innovator: 1.15±0.19 Biosimilar: 1.17±0.15	0.51±0.23 0.53±0.20	20/283 20/296	20/65 20/68	No difference in BCVA or CMT between innovator and biosimilar combined with PD at all timepoints (P>0.05)
Adjunctive rtPA											
Murphy *et al.* *TAPAS* trial	2024	Double masked RCT	56	≥1 DA, nAMD	Baseline ranibizumab + monthly PRN, randomized into sham vs. C_3F_8 vs. rtPA vs. rtPA + C_3F_8	12	sham: 1.01±0.53 C_3F_8: 1.14±0.48 rtPA: 0.88±0.40 rtPA + C_3F_8: 0.83±0.42	0.98±0.58 0.94±0.51 0.51±0.38 0.66±0.44	20/205 20/276 20/152 20/135	20/191 20/174 20/65 20/91	Combined rtPA groups had better 3-month BCVA than those not receiving rtPA (P= 0.02); no BCVA difference when comparing groups that did or did not receive C_3F_8 or individually between all 4 groups; no safety differences across groups
Chotikkakamthorn *et al.*	2025	Retrospective, single center	127	fovea-involving	PD (SF_6 or C_3F_8) + anti-VEGF with or without rtPA	12	rtPA: 1.10±0.51 non-rtPA: 1.28±0.59	Δ logMAR: -0.52±0.10[a] -0.52±0.06[a]	20/252 20/381	–	rtPA did not change VA outcomes but was associated with reduced VH risk (OR 7.03, P=0.004); non-rtPA group had greater decrease in CST at 12-month (P= 0.034)
Wolfram *et al.*	2025	Retrospective, single center	37	nAMD	Triple injection (rtPA, bevacizumab, SF_6)	52.8± 19.2	1.19±0.40[a]	0.62±0.41[a]	20/310	20/83	Triple therapy shows long-term visual and anatomic benefit (P<0.001); RPE tear in 5 (13.5%)

– Indicates item not reported or specified; BCVA, best-corrected visual acuity; CFT/CRT/CMT/CST, central foveal/retinal/macular/subfield thickness; DA, disc area; DD, disc diameter; MT, anti-VEGF monotherapy; nAMD, neovascular age-related macular degeneration; PD, pneumatic displacement; PRN, pro re nata; RCT, randomized control trial; RD, retinal detachment; RPE, retinal pigment epithelium; rtPA, recombinant tissue plasminogen activator; SMH, submacular hemorrhage; VH, vitreous hemorrhage.
[a]Reported in ETDRS letters, converted to logMAR for consistency.

Table 3. Summary of pars plana vitrectomy studies

Author	Year	Study design	Eyes (n)	SMH criteria, etiology	Treatment details	Follow-up (months)	Pretreatment BCVA, logMAR (mean ± SD)	Final BCVA, logMAR (mean ± SD)	Pretreatment BCVA (Snellen)	Final BCVA, (Snellen)	Key findings
Gabrielle *et al.* *STAR* trial	2023	RCT	90	>2 DA, nAMD	PPV + rtPA + SF_6 tamponade vs. PD (SF_6) + rtPA, both with ranibizumab loading	6	PPV: 1.26±0.46[a] PD: 1.26±0.44[a]	0.91±0.49[a] 0.91±0/48[a]	20/364 20/364	20/163 20/163	No significant difference in 6-mo VA between PPV and PD (P=0.776); Overall ocular AE's PPV 12(26.7%) vs. PD 12 (27.3%)
Hillenmayer *et al.*	2024	Retrospective, single center	201	Fovea-involving	1.PD + rtPA 2. Manchester protocol 3. PPV + rtPA 4.PPV only 5. PPV +subretinal lavage	4±6	Group 1: 1.7 Group 2: 1.6±0.8 Group 3: 1.6 Group 4: 2.1 Group 5: 1.9	1.1 1.5 1.7 1.7 1.9	20/1002 20/796 20/796 20/2518 20/1589	20/252 20/632 20/1002 20/1002 20/1589	Only group 2 (Manchester protocol) achieved significant within group gain in AMD patients (P =0.04); PD + rtPA group had the lowest complication rates, while subretinal lavage had highest complication rates
Szeto *et al.*	2024	Retrospective, single center	56	nAMD or PCV	PPV + subretinal cocktail of anti-VEGF + rtPA + gas vs. PD (SF_6 or C_3F_8) ± rtPA + anti-VEGF	12	PPV: 1.62±0.70 PD: 1.46±1.16	PPV: 1.03±0.13 PD: 0.64±0.08	20/834 20/577	20/214 20/87	PPV + subretinal cocktail had superior foveal displacement (87% vs. 37.5%); PD had superior 12-mo BCVA (P=0.04); similar safety profiles
Adjunctive rtPA											
He *et al.*	2023	Meta-Analysis	269	AMD and PCV	Various combined rtPA and anti-VEGF regimens	–	–	Δ logMAR Subretinal rtPA: -0.63 (95% CI: -0.92, -0.34) Intravitreal rtPA: -0.46 (95% CI: -0.69, -0.23)	–	–	rtPA combined with anti-VEGF is effective in improving visual and anatomic outcomes; site of rtPA administration did not affect BCVA improvement (P=0.37) Overall complication rates from 2.4% to 20% across 12 studies
Veritti *et al.*	2024	Meta-Analysis	781	nAMD	Various combined rtPA and anti-VEGF regimens	6	–	Overall Δ logMAR -0.47 (95% CI: -0.56, -0.39)	–	–	rtPA combined with anti-VEGF resulted in significant BCVA improvement and 86% rate of successful displacement; method of rtPA delivery did not affect visual or anatomic outcomes
Simunovic *et al.*	2025	Single-masked, RCT	12	nAMD	1-step vs. 2-step subretinal rtPA (+ SF_6 tamponade and bevacizumab)	3	1-step: 1.57±0.17 2-step: 1.40±0.2	1.1±0.26 1.1±0.32	20/743 20/502	20/252 20/252	There is no significant difference between 1-step and 2-step subretinal rtPA in mean proportion of drug reflux, BCVA change, or CFT change

Table 3 (*Continued*)

Author	Year	Study design	Eyes (n)	SMH criteria, etiology	Treatment details	Follow-up (months)	Pretreatment BCVA, logMAR (mean ± SD)	Final BCVA, logMAR (mean ± SD)	Pretreatment BCVA (Snellen)	Final BCVA, (Snellen)	Key findings
Safran *et al.*	2025	Retrospective, single center	167	Fovea-involving	PPV + subretinal rtPA	43.9 ± 31.4	1.92 ± 0.44	1.58 ± 0.76	20/1664	20/760	Worse final VA was significantly associated with older age, RRD development, poor baseline VA, and glaucoma diagnosis; 15 (9%) developed RRD with macular detachment in 12 (80%) and PVR in 9 (60%)
Adjunctive anti-VEGF											
Ma *et al.*	2024	Retrospective, single center	14	2–5 DD, CST > 250 μm, treatment naive	PPV + subretinal rtPA + intravitreal Conbercept	6	1.37 ± 0.26[a]	0.88 ± 0.30[a]	20/469	20/152	Combined approach with PPV, subretinal rtPA, and Conbercept significantly improved VA and CRT from baseline; Complete regression of SMH in all patients by 3 months
Chen *et al.*	2025	Retrospective, single center	31	PCV	PPV + subretinal rtPA with or without intraoperative anti-VEGF	13.2 ± 7.6	With anti-VEGF: 1.52 Control: 2.30	1.09 ± 0.54 1.46 ± 0.75	20/662 20/3990	20/246 20/577	No significant difference between BCVA when receiving intra-operative anti-VEGF vs. without ($P = 0.110$); no difference in number of anti-VEGF injections given during follow-up period

– Indicates item not reported or specified; AE, adverse event; BCVA, best-corrected visual acuity; CFT/CRT, central foveal/retinal thickness; DA, disc area; DD, disc diameter; FT, foveal thickness; MH, macular hole; MT, Anti-VEGF monotherapy; nAMD, neovascular age-related macular degeneration; PD, pneumatic displacement; PPV, pars plana vitrectomy; RCT, randomized control trial; RD, retinal detachment; RPE, retinal pigment epithelium; rtPA, recombinant tissue plasminogen activator; SMH, submacular hemorrhage; VH, vitreous hemorrhage.
[a]Reported in ETDRS letters, converted to logMAR for consistency.

early VA gains in a small cohort of 31 eyes [31]. Expanding on these findings, in a five-arm cohort, Hillenmayer *et al*. compared PD + intravitreal rtPA, the Manchester protocol, subretinal rtPA, PPV only, and PPV + subretinal lavage and found similar hemorrhage size at last follow-up, however, only the Manchester protocol group had significant VA improvement from baseline [32].

Anatomical SMH clearance may be greater with PPV in some cases. Szeto *et al*. reported that PPV and subretinal cocktail (rtPA + anti-VEGF + gas) resulted in superior foveal displacement compared to PD ± tPA ± anti-VEGF (87% vs. 37.5%, $P<0.001$) despite the PPV group having significantly longer time to operation and more extensive SMH at baseline [33]. However, although both groups had comparable VA at 6 months, final 12-month visual acuity favored the PD group [33]. Taken together, PPV may offer superior anatomical clearance in extensive SMH or delayed presentation, but not necessarily superior visual outcomes as compared to PD.

Other studies focus on the route of rtPA delivery. In a small masked RCT, 1-step subretinal rtPA, which involves use of the therapeutic injection itself to define the subretinal space, vs. 2-step rtPA, where a salt solution is first injected to define the subretinal space and the therapeutic mix is subsequently delivered into the preformed bleb, vision and anatomic outcomes were similar [34]. Studies also showed comparable outcomes between intravitreal rtPA and subretinal rtPA approaches. A meta-analyses by He *et al*. analyzed rtPA-assisted approaches with anti-VEGF treatment and found that both subretinal [mean difference (MD) = −0.63 logMAR, 95% confidence interval (CI): −0.92 to −0.34, $P<0.001$] and intravitreal (MD = −0.46 logMAR, 95% CI: −0.69 to −0.23, $P<0.001$) tPA administration significantly improved BCVA. There was no statistically significant difference between the two administration routes ($P=0.37$), and both groups had high rates of hemorrhage displacement [27]. Another meta-analysis by Veritti *et al*. utilized meta-regression to evaluate outcomes after subretinal rtPA with PPV, PD, and anti-VEGF vs. intravitreal rtPA, PD, and anti-VEGF treatment. Visual outcomes were similar at 1 month ($P=0.173$) and 6 months ($P=0.976$), with similar success rates in SMH displacement ($P=0.721$) [29]. These studies demonstrate that both subretinal and intravitreal rtPA delivery are efficient routes of administration and the benefits of combined rtPA and anti-VEGF regimens for SMH [27,29].

The role of adjunctive anti-VEGF agents at the time of surgery remains unclear. A series of 14 eyes with SMH treated with PPV + subretinal rtPA + intravitreal conbercept yielded significantly improved BCVA and CRT at 6 months, highlighting the efficacy of this anti-VEGF in treating SMH [35]. Other studies have found no added visual gains or reduced injection burden with intraoperative anti-VEGF [36]. In a secondary analysis, Veritti *et al*. reports that the site of anti-VEGF delivery (subretinal vs. intravitreal) had no impact on VA outcomes in patients treated with subretinal rtPA [29]. Overall, while the role of postoperative anti-VEGF for disease control is evident, its utility intraoperatively is still debatable.

Despite potential benefits, surgical intervention introduces additional risk. A large retrospective study of 167 eyes undergoing PPV and subretinal tPA found that postoperative RD occurred in 9% of eyes [37▪]. Despite high reattachment rates, 60% of patients developed PVR, and visual recovery was limited, emphasizing careful patient selection when considering PPV over less invasive methods [37▪]. Additionally, older age, worse baseline VA, and a history of glaucoma were all associated with poorer prognosis [37▪]. Nevertheless, other recent studies demonstrate comparable safety profiles between PPV and PD in line with previously reported rates of complications [30]. Gabrielle *et al*. reports that while rates of SMH recurrence were higher in their PD group and RD rates were higher in their PPV group, there was no significant difference between the two arms over 6 months and overall ocular adverse event rates were also similar (26.7% vs. 27.3%) [30]. Szeto *et al*. reported a higher reoperation rate with PD (20% vs. 12%) that was not statistically significant [33]. Both studies underscore that surgery remains effective and generally safe when selecting patients appropriately.

Controversies and challenges

Despite growing evidence, there continues to be no universal standard for the management of SMH. Choice of treatment continues to rely on clinician judgment informed by hemorrhage size, chronicity, and individual patient factors.

Efforts to develop treatment frameworks using OCT and autofluorescence have not been widely adopted, reflecting high variability in real-world management [12]. Further, interpretation of the literature can also be challenging as there is also no standardized definition of successful SMH displacement, complicating comparisons and reducing the strength of pooled analyses. The timing of the intervention remains another challenge in treatment. Earlier intervention has been associated with improved outcomes [10▪,23]. However, in practice, delayed presentation, referral patterns, and resource limitations can limit the feasibility of early intervention.

Regarding the safety profile, there is huge variability in incidence rates of major complications

across studies [27], which further complicates treatment selection. Some studies, such as Safran *et al.*, reported higher postoperative RD after PPV and subretinal rtPA [37▪]. however, other recent meta-analyses found no significant difference in complication rates between subretinal rtPA and intravitreal rtPA [27,29]. Overall, this wide variability suggests that complication risk may be more influenced by individual hemorrhage characteristics and case selection rather than by the treatment modality itself.

Standardized outcome definitions and prospective comparative trials are still needed to clarify optimal treatment strategies. Additionally, there remains a gap in research specific to SMH secondary to causes other than nAMD and PCV.

Future directions and ongoing trials

Ongoing studies are helping to address current uncertainties in SMH management. Most notable is the European TIGER study launched in 2022, which is an ongoing RCT that compares vitrectomy, subretinal rtPA, gas tamponade, and intravitreal aflibercept against aflibercept monotherapy in patients with SMH secondary to nAMD [38]. In addition to better clarifying the role of combination surgery regimens, the trial also incorporates health-economic analyses to better assess practical applicability, filling a major evidence gap.

Imaging is also expected to play a growing role in guiding prognosis and treatment planning. Although fundus autofluorescence (FAF) is traditionally used to evaluate RPE integrity and monitor for atrophic changes later in management, Venkatesh *et al.* suggest its potential prognostic value in the acute phase [39]. They propose that well defined homogeneous hypoautofluorescence patterns in acute hemorrhage may suggest a more favorable response to displacement [39]. On OCT imaging of RAM-related SMH, Miyamoto *et al.* described "foveal mountain peak sign" as a potential predictor of macular hole formation, demonstrating how imaging biomarkers can help with risk stratification [40].

CONCLUSION

While new research continues to provide further insight, the management of submacular hemorrhage remains individualized. Anti-VEGF therapy continues to be a foundational aspect of SMH treatment while PD, PPV, and rtPA expand therapeutic options, especially for cases with larger SMHs. Combination regimens allow physicians to leverage the benefits of each modality while still limiting unnecessary risk. Yet, no single approach has proven definitively superior, highlighting the importance of individual patient factors and physician judgement. Ongoing trials are expected to inform the development of standardized algorithms. Future work should aim to refine patient selection methodology and establish more standardized outcome definitions.

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Conflicts of interest

There are no conflicts of interest.

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