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Submacular Hemorrhage during Neovascular Age-Related Macular Degeneration: A Meta-Analysis and Meta-Regression on the Use of tPA and Anti-VEGFs

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Keywords
Age-related macular degeneration · Anti-vascular endothelial growth factor · Pneumatic displacement · Submacular hemorrhage · Tissue plasminogen activator

Abstract
Background: Submacular hemorrhage (SMH) associated with neovascular age-related macular degeneration (nAMD) precipitates rapid visual decline and impacts quality of life. Treatments vary, but combined recombinant tissue plasminogen activator (tPA) and anti-vascular endothelial growth factor (anti-VEGF) therapy has gained prominence as a viable treatment option. ***Objectives:*** This study aimed to evaluate the efficacy of the combination of tPA and anti-VEGF. ***Methods:*** We conducted a systematic review meta-analysis following PRISMA guidelines, focusing on studies examining tPA and anti-VEGF therapy in SMH secondary to nAMD. Outcomes measured were change in best-corrected visual acuity (BCVA) and success rate of SMH displacement. Meta-regression assessed the relative efficacy of intravitreal and subretinal delivery. ***Results:*** Out of 257 initial reports, 22 studies involving 29 patient populations met inclusion criteria. Our analysis showed significant improvement in BCVA and a high rate of successful SMH displacement with combined tPA and anti-VEGF therapy. No significant differences were found between subretinal and intravitreal tPA administration. Furthermore, when evaluating the effects of subretinal versus intravitreal anti-VEGF administration in patients treated with subretinal tPA, the results indicated similar efficacy. ***Conclusions:*** Combined tPA and anti-VEGF therapy is effective in managing SMH in nAMD patients, significantly improving visual acuity and SMH displacement. The location of tPA and anti-VEGF delivery did not significantly impact outcomes.

Introduction

Submacular hemorrhage (SMH) represents a severe and devastating complication in the context of neovascular age-related macular degeneration (nAMD) [1]. The presence of SMH results in a rapid decline in visual acuity and significantly hampers the patient's quality of life [2]. Besides the direct cytotoxic effects on the retina, SMH can also hinder effective delivery and action of anti-VEGF therapy. A plethora of treatment

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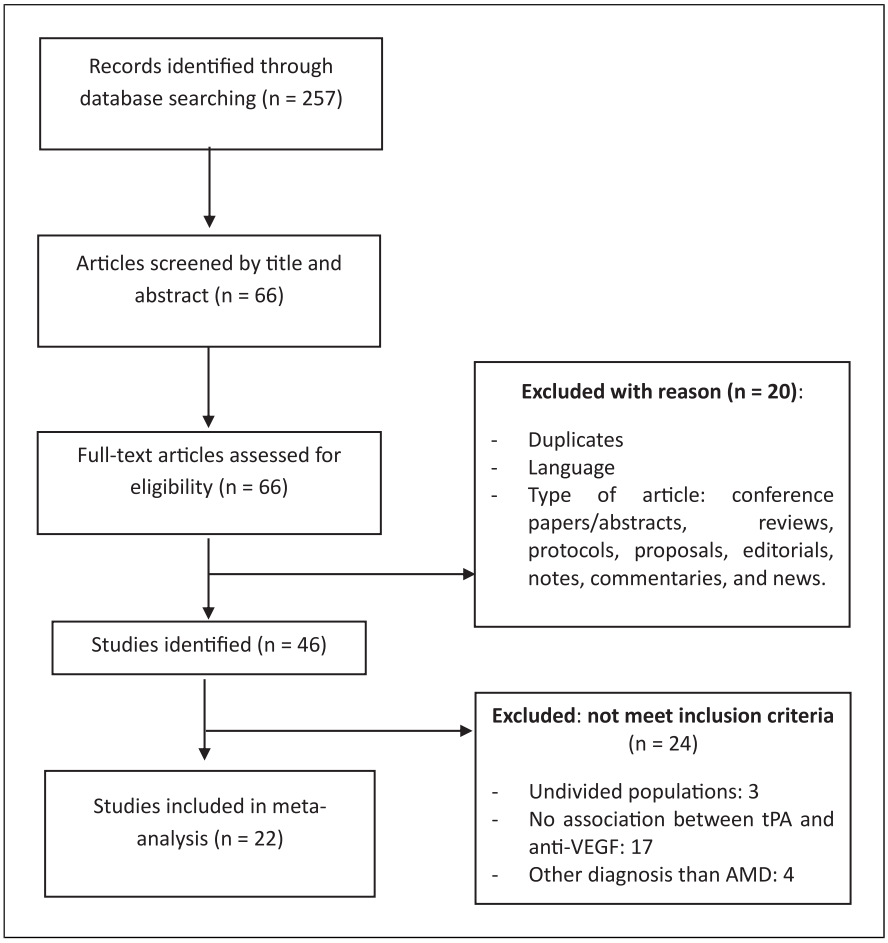


Fig. 1. Study selection flowchart.

modalities have been explored over the years, including pneumatic displacement (PD), laser photocoagulation, and surgical intervention [3]. However, a growing body of evidence suggests that the combination of recombinant tissue plasminogen activator (tPA) and anti-vascular endothelial growth factor (anti-VEGF) agents may offer a synergistic approach in the management of this complex condition [4]. tPA is known for its fibrinolytic properties, facilitating clot dissolution and thereby aiding in the displacement of submacular blood [5]. On the other hand, anti-VEGF agents act by inhibiting the angiogenic factors responsible for choroidal neovascularization, the underlying etiology of nAMD [6]. This dual-action strategy addresses both the causative and consequential aspects of the disease, offering a comprehensive treatment approach. Despite the promise held by this combined modality, there remains a paucity of robust, aggregated data to definitively establish its efficacy profile. The administration method – either a more invasive pars plana vitrectomy (PPV) for subretinal tPA administration or a less invasive intravitreal approach – is still debated. The relative efficacy of these strategies need further clarification, demanding more systematic research. The choice between these approaches depends on various factors, including the size and location of the SMH, patient's overall health, and the surgeon's expertise. Our meta-analysis aims to address this gap by systematically reviewing prospective and retrospective studies that have assessed the combined use of tPA and anti-VEGF in the treatment of SMH secondary to nAMD. Using a meta-regression approach, we seek to answer the following clinically pertinent questions:

1. Does combining tPA and anti-VEGF therapy benefit patients with SMH due to nAMD?
2. Which is more effective: PPV for subretinal tPA administration or a less invasive intravitreal approach?
3. If tPA is administered subretinally, should anti-VEGFs be delivered in the same manner?

Table 1. Baseline characteristics of included populations

Author	Publication (year)	Eyes, *n*	Country	Age, mean (SD), years	BCVA, mean (SD), logMAR	tPA	Anti-VEGF	NOS
Arias [11] (1)	2010	7	Spain	79.6 (8.6)	1.44 (0.11)	Intravitreal	Intravitreal	5
Arias [11] (2)	2010	8	Spain	79.6 (8.6)	1.69 (0.001)	Subretinal	Intravitreal	5
Avci et al. [12]	2021	30	Turkey	73.3 (8.2)	2.11 (0.84)	Subretinal	Subretinal	5
Boichè et al. [13]	2019	26	France	78 (8)	2.4 (0.6)	Subretinal	Intravitreal	5
Boral et al. [14]	2023	62	India	64.1 (10.2)	2.09 (0.68)	Subretinal	Subretinal	5
Chakraborty et al. [15]	2022	3	India	71.7 (10.3)	1.23 (0.33)	Intravitreal	Intravitreal	4
de Silva et al. [16]	2016	8	UK	81 (4.3)	1.67 (0.47)	Intravitreal	Intravitreal	5
Erdogan et al. [17]	2020	9	Turkey	72.8 (10.2)	2.46 (0.64)	Subretinal	Intravitreal	5
Gabrielle et al. [18] (1)	2023	45	France	84.3 (8.3)	1.26 (0.46)	Subretinal	Intravitreal	7
Gabrielle et al. [18] (2)	2023	44	France	82.3 (8.0)	1.26 (0.44)	Intravitreal	Intravitreal	7
Grohmann et al. [19] (1)	2020	32	Germany	85.4	1.41 (0.48)	Intravitreal	Intravitreal	7
Grohmann et al. [19] (2)	2020	42	Germany	85.4	1.46 (0.54)	Subretinal	Intravitreal	7
Grohmann et al. [19] (3)	2020	11	Germany	85.4	1.63 (0.53)	Intravitreal	Intravitreal	7
Guthoff et al. [20]	2011	12	Germany	81.7	0.92 (0.89)	Intravitreal	Intravitreal	7
Iannetta et al. [21]	2021	25	Italy	81.3 (6.8)	1.81 (0.33)	Subretinal	Intravitreal	5
Iglicki et al. [22] (1)	2023	41	Argentina	80.5 (5.5)	0.65 (0.13)	Subretinal	Subretinal	7
Iglicki et al. [22] (2)	2023	41	Argentina	80.5 (5.5)	0.69 (0.96)	Subretinal	Subretinal	7
Iglicki et al. [22] (3)	2023	41	Argentina	80.5 (5.5)	0.74 (0.81)	Subretinal	Subretinal	7
Iglicki et al. [23] (4)	2022	41	Argentina	80.5 (5.5)	0.651 (0.134)	Subretinal	Subretinal	7
Iglicki et al. [23] (5)	2022	39	Argentina	80.3 (3.7)	0.749 (0.085)	Subretinal	Intravitreal	7
Kitagawa et al. [24]	2022	64	Japan	72 (10)	0.54 (0.38)	Intravitreal	Intravitreal	5
Kumar et al. [25]	2016	10	India	66.9 (7.3)	1.45 (0.3)	Subretinal	Subretinal	5
Lee et al. [26]	2016	25	South Korea	67.6 (8.9)	1.09 (0.77)	Intravitreal	Intravitreal	5
Limon et al. [27]	2023	8	Turkey	72.4	2.23 (0.14)	Subretinal	Subretinal	5
Ogata et al. [28]	2022	13	Japan	77.2	0.90 (0.12)	Subretinal	Subretinal	5
Patikulsila et al. [29]	2022	5	Thailand	62.6 (5.2)	1.78 (0.53)	Subretinal	Intravitreal	5
Ramesh et al. [30]	2022	6	India	NA	1.46 (0.43)	Subretinal	Intravitreal	4
Rickman et al. [31]	2021	17	Germany	81.7 (5.2)	1.37 (0.39)	Intravitreal	Intravitreal	7
Treumer et al. [32]	2010	12	Germany	81.5 (5.4)	1.87 (0.89)	Subretinal	Subretinal	5

NOS represents the score of the methodological quality of the included studies according to the modified version (nine-star scoring system). BCVA, best-corrected visual acuity; *n*, number; NA, not available; NOS, Newcastle-Ottawa Scale; SD, standard deviation; logMAR, logarithm of the minimum angle of resolution; tPA, tissue plasminogen activator; VEGF, vascular endothelial growth factor.

Methods

Search Strategy and Registration

This review, meta-analysis, and meta-regression are compliant with the PRISMA guidelines and are aligned with the tenets of the Declaration of Helsinki [7]. Searches were executed on Ovid MEDLINE, Embase, and Cochrane Library spanning the period of January 2006 to September 2023. The primary keywords that guided this search included submacular hemorrhage, sub-macular hemorrhage, SMH; recombinant tissue plasminogen activator, rt-PA, rtPA, r-tPA, rTPA, tPA; along with the terms anti-vascular endothelial growth factor, anti-VEGF, ranibizumab, aflibercept, brolucizumab, and bevacizumab.

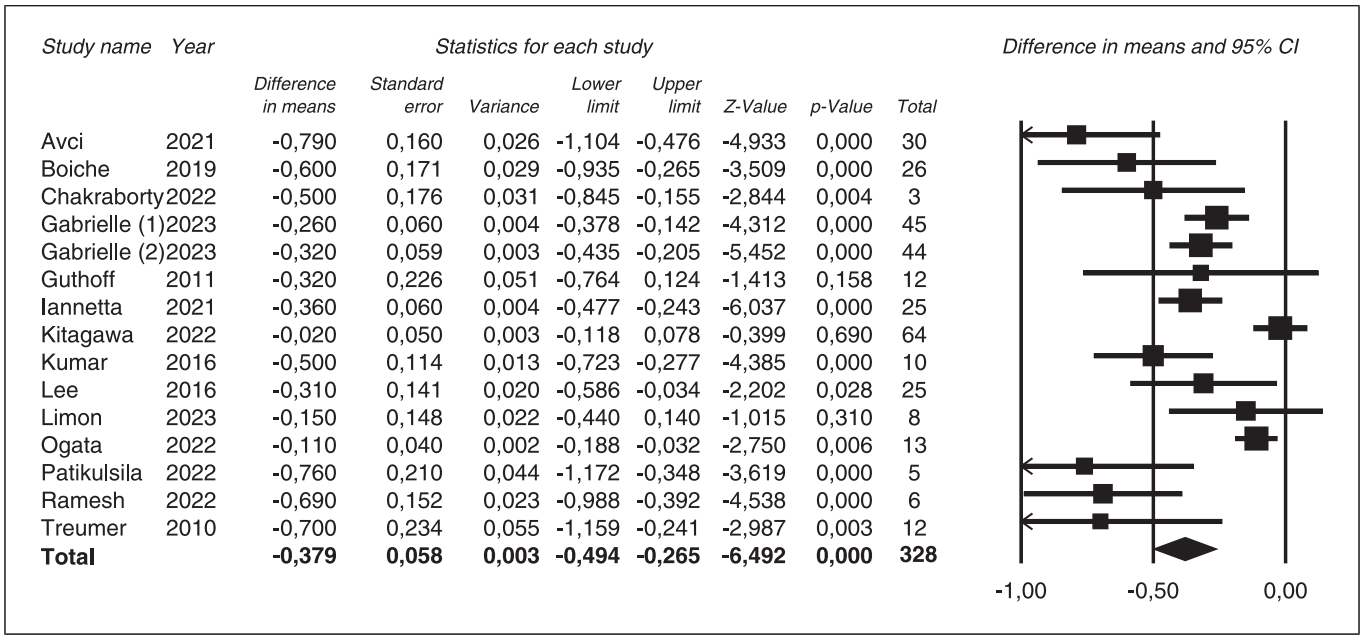


Fig. 2. Forest plot of primary analysis illustrating changes in visual acuity at 1 month. Visual acuity measurements are presented in logMAR.

Eligibility Criteria

Articles underwent an initial screening based on titles and abstracts, followed by a comprehensive full-text review. We exclusively focused on studies exploring combined anti-VEGF and tPA interventions for SMH in nAMD patients. Randomized clinical trials and real-world prospective and retrospective clinical studies were included. Only studies published in peer-reviewed journals and in the English language were deemed eligible. Studies which did not present the minimum required data for effective effect size evaluation were excluded, as were those presenting duplicated data. Reviewers (D.M. and S.M.) worked independently to screen and select articles. Disparities between reviewers' decisions were adjudicated by a third party (D.V.).

Data Extraction and Quality Assessment

Data were extracted and compiled using a standardized form. This form encompassed key details such as the first author's name, publication year, country of origin, study design, number of participants, and essential data on the study population (including age, sex, SMH duration, baseline visual acuity, SMH size, and specific intervention measures). The primary efficacy outcome was change in best-corrected visual acuity (BCVA) from baseline to 1 month (early outcomes) and 6 months (late outcomes) post-intervention. For studies lacking 6-month data, the BCVA outcome at the next closest follow-up timepoint was used in the analysis. BCVA was reported using the logMAR scale. Secondary measures were the incidence of successful SMH displacement. The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality and risk of bias of the included studies [8].

Statistical Analyses

The primary objective of the present meta-analysis was to derive a pooled estimate for effectiveness (defined as BCVA change from baseline). When necessary, variables of interest were converted to logMAR BCVA values [9]. Fixed-effects and random-effects models were used to produce estimates. Heterogeneity was assessed using the I^2 statistic [10]. Publication bias was evaluated by Egger's linear regression and visualized with funnel plots. A meta-regression analysis was subsequently conducted. Primary moderators were pre-selected based on existing evidence. Moderators included in the meta-regression were baseline BCVA, mean age at baseline, mean SMH duration, and specific intervention measures, such as the location of tPA and anti-VEGF administration.

Results

Study Selection and Characteristics

The initial search yielded 257 reports. After screening titles and abstracts and removing duplicates, 66 potentially relevant papers were identified. The full texts of these articles were subsequently extracted and rigorously assessed for eligibility. Ultimately, the final analysis incorporated 22 studies, which collectively described 29 diverse patient populations that met the inclusion criteria. The flowchart outlining the selection process is presented in Figure 1. Characteristics of the 29 populations selected for statistical analysis are detailed in Table 1 [11–32]. Few of these studies comprised multiple heterogeneous

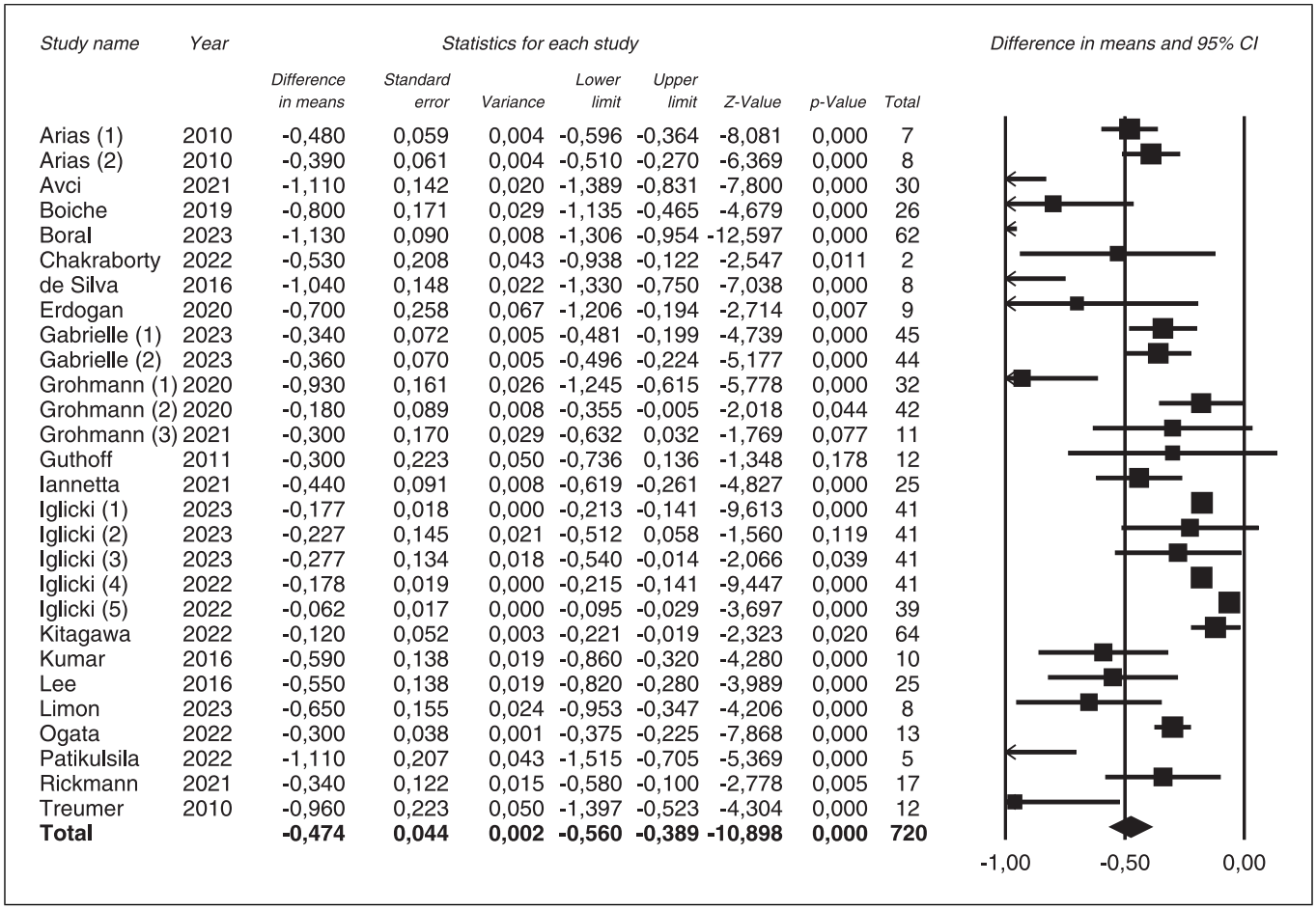


Fig. 3. Primary analysis forest plot showing long-term visual acuity. Visual acuity is expressed in logMAR.

groups; for the purposes of this analysis, each group was treated as a distinct population. Most of the included studies were of an observational or real-life nature, characterized by single-arm interventional designs and retrospective chart reviews. Among the 22 studies, 1 was a randomized clinical trial, 1 was a prospective cohort study, and 20 were retrospective cohort studies. The sample size across these studies varied considerably, ranging from 3 to 64 eyes, with a total of 781 eyes enrolled.

Primary Analysis: Efficacy of Combined tPA Administration and VEGF Inhibition

To evaluate the clinical effectiveness of combined tPA and anti-VEGF therapy in patients with SMH secondary to nAMD, we performed three separate meta-analyses, focusing on variations in follow-up durations, specifically distinguishing between early and late outcomes, and the rate of successful SMH displacement. Notable heterogeneity characterized the 1-month follow-up studies (I^2 = 82.255%, $p < 0.001$), prompting the application of a random-effects model. This model unveiled a significant enhancement in BCVA, evidenced by a change of −0.379 logMAR (95% CI: −0.494; −0.265, $p < 0.001$) (shown in Fig. 2). Similarly, a pronounced heterogeneity was detected in the late follow-up findings (I^2 = 92.638%, $p <$ 0.001), leading to the adoption of another random-effects model. This subsequent analysis marked a change of −0.474 in logMAR (95% CI: −0.560; −0.389, $p < 0.001$) (shown in Fig. 3). In evaluating long-term rates of successful SMH displacement, a moderate heterogeneity was observed (I^2 = 58.997%, $p < 0.001$), warranting the continued use of the random-effects model. This yielded a success rate of 86% in SMH displacement (95% CI: 76–93%) (shown in Fig. 4). A leave-one-out sensitivity analysis corroborated the robustness of these findings, with no single study exerting a substantial impact on the overall effect size. Collectively, these outcomes underline

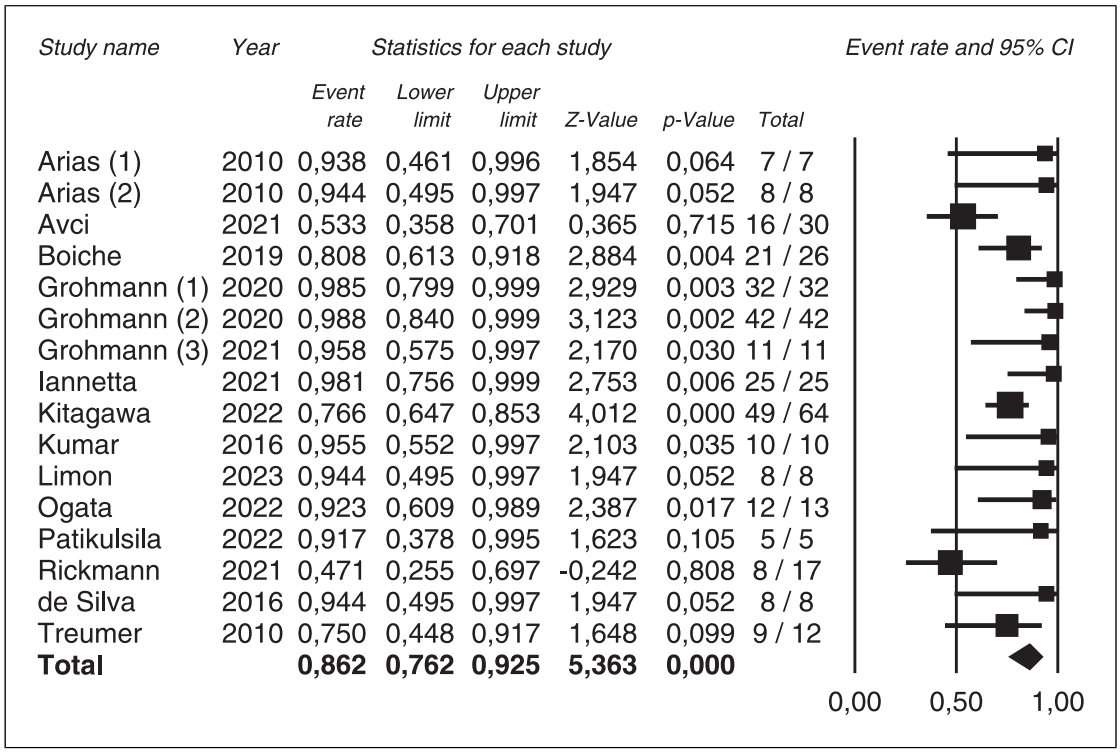


Fig. 4. Forest plot of primary analysis illustrating the success rate of SMH displacement.

that the combination of tPA and anti-VEGF therapy is effective in improving the visual acuity of nAMD patients with SMH.

Secondary Analysis

Comparing Subretinal to Intravitreal Treatment Approaches

Utilizing meta-regression, we evaluated the effectiveness of a surgical approach combining PPV with subretinal tPA, PD, and anti-VEGF versus a minimally invasive strategy employing intravitreal tPA, PD, and anti-VEGF. At the one-month mark, the analysis yielded no statistically significant difference ($p = 0.173$), albeit with a slight inclination toward the surgical procedure, as evidenced by a −0.18 logMAR coefficient (95% CI: −0.43 to +0.08) (shown in Fig. 5a). An extended analysis of long-term outcomes mirrored these findings, recording no substantial distinction ($p = 0.976$) (shown in Fig. 5b). The success rate in SMH displacement was not significantly different between the two techniques ($p = 0.721$).

Subretinal or Intravitreal Anti-VEGF?

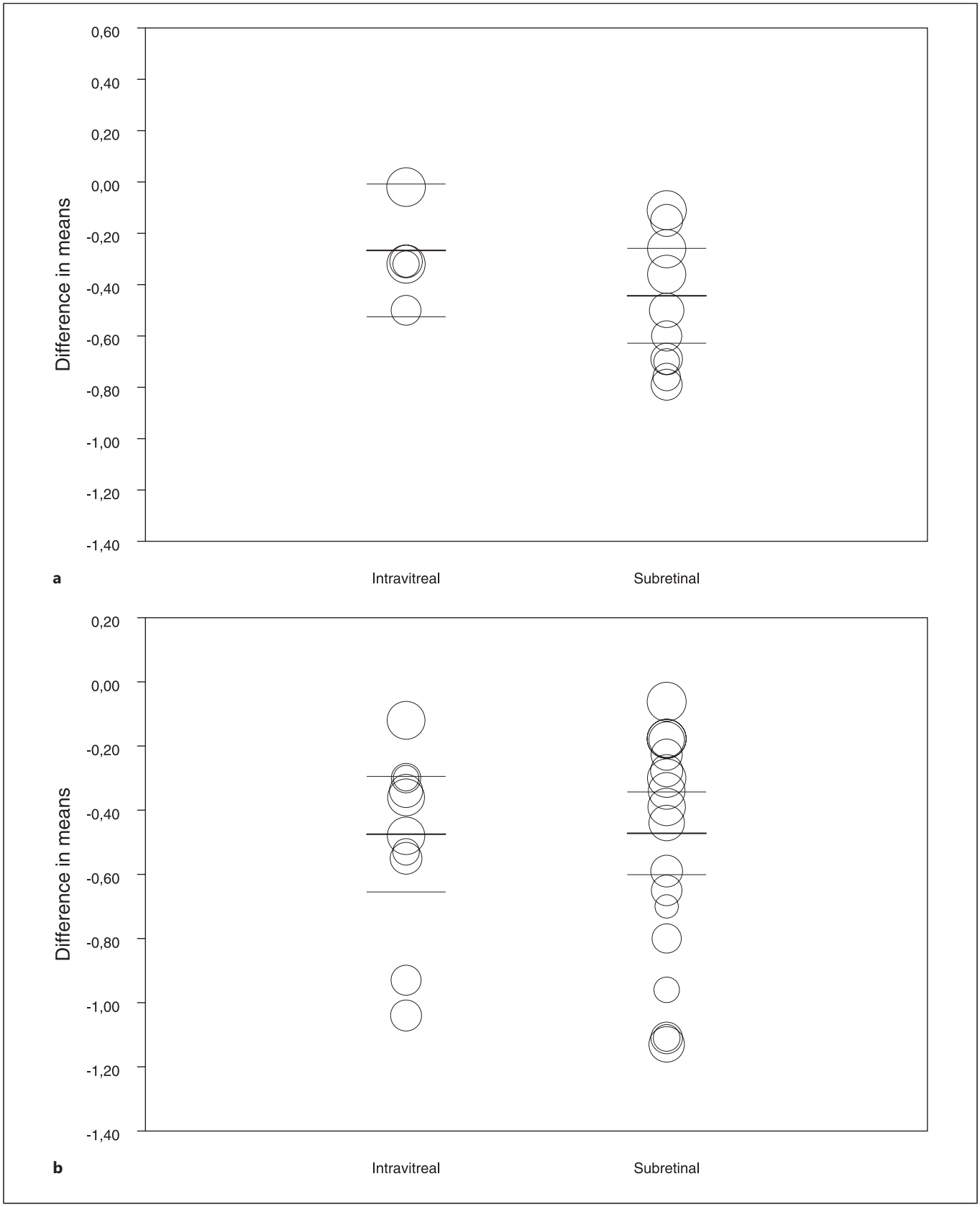
We applied meta-regression to address an additional critical clinical query: is subretinal anti-VEGF superior to intravitreal anti-VEGF among patients undergoing subretinal tPA and PPV? In an analysis of 498 eyes from 18 distinct populations treated with subretinal tPA, no significant statistical difference was observed at both early ($p = 0.6$) and late ($p = 0.65$) timepoints. The long-term coefficient was −0.06 logMAR (95% CI: −0.29 to +0.17) (shown in Fig. 6), indicating a non-significant preference for intravitreal administration.

Other Moderators

Several additional moderators were examined for potential influence on the outcomes. These included proportion of female gender, baseline mean age, interval to surgery, specific anti-VEGF drug administered, and the type of gas employed for PD. None of these factors demonstrated a significant impact on the study results.

Sensitivity Analysis and Risk of Bias

Funnel plot asymmetry was seen in the present meta-analysis. Egger's linear regression (intercept = −3.66, $p < 0.001$) and Begg's rank correlation test (Kendall's $\tau = -0.276$, $p = 0.003$) also suggest the existence of publication bias. After imputing missing studies in the funnel plot, adjustment of effect size for possible publication bias using the trim-and-fill correction results in decreased, albeit still highly significant estimate of pooled mean difference (adjusted = −0.36 logMAR; 95% CI:



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−0.44; −0.28; $p < 0.0001$). A "one-study-removed" technique and a "cumulative meta-analysis" technique were used to evaluate the potential influence of a small-study effect. Both techniques express negative results.

Discussion

SMH is one of the most visually devastating ocular conditions arising as a complication of nAMD. The acute buildup of blood under the fovea leads to irreversible harm to photoreceptors and retinal pigment epithelium cells, frequently resulting in permanent vision loss if left untreated [1]. The management of SMH secondary to nAMD remains a clinically challenging scenario due to the lack of large, controlled clinical trials evaluating optimal treatment approaches [10–31]. This meta-analysis strongly supports the use of combined tPA and anti-VEGF therapy for SMH in nAMD patients. The pooled analysis of 29 populations demonstrated statistically significant improvements in BCVA of 0.38 logMAR in the early term and 0.47 logMAR in the long term. Additionally, we observed an 86% success rate in displacing SMH. These findings align with prior research advocating the synergistic benefits of the fibrinolytic properties of tPA and the anti-angiogenic effects of VEGF inhibitors in comprehensively managing SMH [4]. A key finding is that the method of tPA delivery, whether subretinal or intravitreal, did not significantly affect visual outcomes. This finding aligns with earlier studies suggesting that although subretinal delivery of tPA might be more

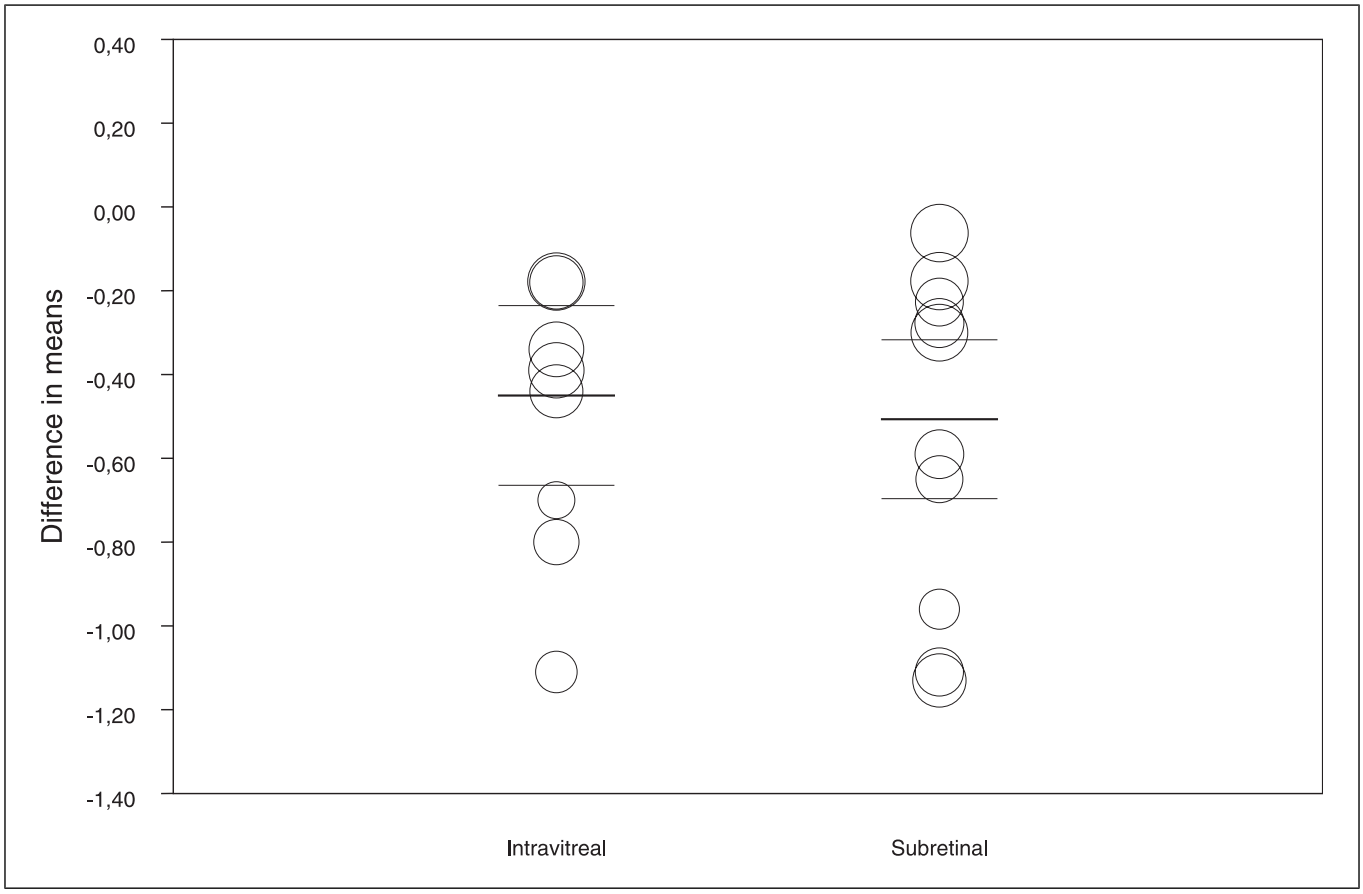

Fig. 6. Secondary analysis meta-regression showing regression of difference in mean visual acuity changes on anti-VEGF administration location among patients that received subretinal tPA.

Fig. 5. Secondary analysis meta-regression showing the impact of tPA administration location on mean visual acuity changes, differentiating between early (**a**) and late outcomes (**b**).

targeted, it does not necessarily lead to higher success rates or better visual outcomes compared to intravitreal administration [29–31]. However, our aggregate data analysis was unable to account for individual factors like hemorrhage size and chronicity that may influence clinical decision-making. For instance, a crucial aspect our study did not evaluate is the size of the SMH, an element that existing literature underscores as pivotal in therapeutic strategy selection. Guidance from the Vision Academy's consensus document specifically recommends surgical intervention with subretinal tPA administration and anti-VEGF injection primarily for severe cases of SMH, with the decision being based on factors such as the hemorrhage's thickness and location [33]. On this subject, a subanalysis of the STAR trial showed the impact of SMH size and thickness on treatment outcomes. Findings indicated no significant influence of SMH size and thickness on the comparative effectiveness of PPV with subretinal tPA, PD, and intravitreal ranibizumab versus PD with intravitreal tPA and ranibizumab, suggesting that these morphological characteristics of SMH may not dictate treatment choice [18]. In future, larger studies are needed to better investigate whether hemorrhage severity indicators can guide optimal patient selection for varied tPA approaches. Among patients treated with subretinal tPA, the site of anti-VEGF delivery also did not impact visual acuity outcomes, though a non-significant inclination toward intravitreal injection was observed. Moreover, it should be noted that the optimal dosage and volume of anti-VEGF agents for subretinal delivery remains unclear, presenting an avenue for future pharmacokinetic research.

Although beyond the objectives of this meta-analysis, when determining the most suitable therapeutic choice, it is judicious to also consider the safety profile of the two approaches. Regarding the incidence ranges of major complications, patients treated with PPV and subretinal tPA exhibited recurrent SMHs in 0–22%, vitreous hemorrhages in 0–20%, and retinal detachments in 0–11.8%. Patients receiving intravitreal tPA injection displayed recurrent SMHs in 0–13.6%, vitreous hemorrhages in 0–25%, and retinal detachments in 0–5% [4]. This huge variability in complication rates underscores the critical need for a careful evaluation of the risk-to-benefit ratio of each approach, ensuring that therapeutic decisions are tailored to the individual patient's circumstances. Within the context of safety assessments, data from the randomized STAR trial merits attention. In the PPV group treated with subretinal tPA, adverse events were reported at a rate of 27%, encompassing retinal detachment (9%), vitreous hemorrhage (11%), and recurrent SMH (4%). Conversely, in the group receiving intravitreal tPA injections and PD, the overall occurrence of adverse events matched that of the PPV group at 27%, with specific incidences of vitreous hemorrhage (11%) and recurrent SMH (14%); no cases of retinal detachment were observed [18]. Beyond clinical outcomes, it is also crucial to consider treatment effects on quality of life. Despite improvements in visual acuity and hemorrhage management, it has been shown that neither approach significantly enhances quality of life over 6 months [18]. Limitations of this meta-analysis include between-study heterogeneity, risks of ecological fallacy wherein group-level associations may not reflect individual-level relationships, and potential publication bias. Furthermore, while we recognize postoperative positioning as a potential variable of interest that could influence treatment outcomes, its integration into our meta-analysis was impeded by the substantial variability in postoperative positioning protocols across the studies included, coupled with a lack of detailed, standardized information. Our findings highlight the need for large prospective clinical trials using stringent inclusion criteria to reduce variability. In this context, it is worth mentioning the TIGER trial, designed to evaluate whether SMH surgery, combined with subretinal tPA and intravitreal gas, provides more benefit compared to VEGF inhibitors alone in treating SMH due to neovascular AMD, with its outcomes eagerly anticipated. Research endeavors of this nature are critical to develop individualized treatment guidelines integrating SMH morphological features and optimized, personalized pharmacotherapeutic protocols [34]. This precision medicine approach could lead to better visual outcomes for patients with this severe nAMD complication. In summary, our findings provide evidence supporting combined tPA and anti-VEGF therapy for SMH management in nAMD patients. While no major difference was found between surgical and intravitreal tPA approaches, individualized decision-making integrating patient factors is recommended. Further research should address limitations of aggregate data analysis and optimize treatment protocols.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

Daniele Veritti: consultant for Bayer, Novartis, and Roche; Valentina Sarao: consultant for I-Care; Deborah Martinuzzi and Sara Menzio: no conflicts of interest to declare; and Paolo Lanzetta: consultant for Aerie, Allergan, Apellis, Bausch & Lomb, Bayer, Biogen, Boehringer Ingelheim, I-Care, Genentech, Novartis, Ocular Therapeutix, Outlook Therapeutics, and Roche.

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Author Contributions

Daniele Veritti, Valentina Sarao, Deborah Martinuzzi, Sara Menzio, and Paolo Lanzetta have satisfied the four criteria of authorship detailed by International Committee of Medical Journal Editors (ICMJE) recommendations. All authors contributed substantially to one or more of the following aspects of the manuscript: conception of the study, data acquisition, statistical analysis, drafting, revision for intellectual content, and final approval.

Data Availability Statement

All generated data are included in this paper. Further inquiries are to be directed to the corresponding author.

References

1 Avery RL, Fekrat S, Hawkins BS, Bressler NM. Natural history of subfoveal subretinal hemorrhage in agerelated macular degeneration. Retina. 1996;16(3):183–9. https://doi.org/10.1097/00006982-199616030-00001.
2 Bennett SR, Folk JC, Blodi CF, Klugman M. Factors prognostic of visual outcome in patients with subretinal hemorrhage. Am J Ophthalmol. 1990;109(1):33–7. https://doi.org/10.1016/s0002-9394(14)75575-8.
3 Stanescu-Segall D, Balta F, Jackson TL. Submacular hemorrhage in neovascular age-related macular degeneration: a synthesis of the literature. Surv Ophthalmol. 2016;61(1):18–32. https://doi.org/10.1016/j.survophthal.2015.04.004.
4 He X, Cao W, Wang Z, Zhang N, Xu K, Yu L, et al. Efficacy evaluation of tissue plasminogen activator with anti-vascular endothelial growth factor drugs for submacular hemorrhage treatment: a meta-analysis. J Clin Med. 2023;12(3):1035. https://doi.org/10.3390/jcm12031035.
5 Rijken DC. Plasminogen activators and plasminogen activator inhibitors: biochemical aspects. Baillieres Clin Haematol. 1995;8(2):291–312. https://doi.org/10.1016/s0950-3536(05)80269-0.
6 Shienbaum G, Garcia Filho CA, Flynn HW, Nunes RP, Smiddy WE, Rosenfeld PJ. Management of submacular hemorrhage secondary to neovascular age-related macular degeneration with anti-vascular endothelial growth factor monotherapy. Am J Ophthalmol. 2013;155(6):1009–13. https://doi.org/10.1016/j.ajo.2013.01.012.
7 Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Open Med. 2009;3(3):e123–30.
8 Lo CK, Mertz D, Loeb M. Newcastle-ottawa Scale: comparing reviewers' to authors' assessments. BMC Med Res Methodol. 2014;14:45. https://doi.org/10.1186/1471-2288-14-45.
9 Khoshnood B, Mesbah M, Jeanbat V, Lafuma A, Berdeaux G. Transforming scales of measurement of visual acuity at the group level. Ophthalmic Physiol Opt. 2010;30(6):816–23. https://doi.org/10.1111/j.1475-1313.2010.00766.x.
10 Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60. https://doi.org/10.1136/bmj.327.7414.557.
11 Arias L. Transconjunctival sutureless vitrectomy with tissue plasminogen activator, gas and intravitreal bevacizumab in the management of predominantly hemorrhagic age-related macular degeneration. OPTH. 2010;67:67. https://doi.org/10.2147/opth.s8635.
12 Avcı R, Mavi Yıldız A, Çınar E, Yılmaz S, Küçükerdönmez C, Akalp FD, et al. Subretinal coapplication of tissue plasminogen activator and bevacizumab with concurrent pneumatic displacement for submacular hemorrhages secondary to neovascular age-related macular degeneration. Turk J Ophthalmol. 2021;51(1):38–44. https://doi.org/10.4274/tjo.galenos.2020.72540.
13 Boiché M, Angioi-Duprez K, Conart JB, Berrod JP. Treatment of hematomas in age related macular degeneration by vitrectomy and subretinal injection of r-tPA: preliminary results. J Fr Ophtalmol. 2019;42(9):e391–7. https://doi.org/10.1016/j.jfo.2019.07.002.
14 Boral SK, Agarwal D, Das A, Chakraborty D, Mandal S. Real-world outcomes and complications of different surgical approaches for significant submacular haemorrhages. Indian J Ophthalmol. 2023;71(5):2045–52. https://doi.org/10.4103/ijo.IJO_1987_22.
15 Chakraborty D, Sheth JU, Mondal S, Boral S. Role of intravitreal brolucizumab with intravitreal rtPA and pneumatic displacement for submacular hemorrhage: a case series. Am J Ophthalmol Case Rep. 2022;25:101390. https://doi.org/10.1016/j.ajoc.2022.101390.
16 De Silva SR, Bindra MS. Early treatment of acute submacular haemorrhage secondary to wet AMD using intravitreal tissue plasminogen activator, C3F8, and an anti-VEGF agent. Eye. 2016;30(7):952–7. https://doi.org/10.1038/eye.2016.67.
17 Erdogan G, Kirmaci A, Perente I, Artunay O. Gravitational displacement of submacular haemorrhage in patients with age-related macular disease. Eye. 2020;34(6):1136–41. https://doi.org/10.1038/s41433-019-0720-8.
18 Gabrielle PH, Delyfer MN, Glacet-Bernard A, Conart JB, Uzzan J, Kodjikian L, et al. Surgery, tissue plasminogen activator, anti-angiogenic agents, and age-related macular degeneration study: a randomized controlled trial for submacular hemorrhage secondary to age-related macular degeneration. Ophthalmology. 2023;130(9):947–57. https://doi.org/10.1016/j.ophtha.2023.04.014.
19 Grohmann C, Dimopoulos S, Bartz-Schmidt KU, Schindler P, Katz T, Spitzer MS, et al. Surgical management of submacular hemorrhage due to n-AMD: a comparison of three surgical methods. Int J Retin Vitr. 2020;6(1):27. https://doi.org/10.1186/s40942-020-00228-x.
20 Guthoff R, Guthoff T, Meigen T, Goebel W. Intravitreous injection of bevacizumab, tissue plasminogen activator, and gas in the treatment of submacular hemorrhage in age-related macular degeneration. Retina. 2011;31(1):36–40. https://doi.org/10.1097/IAE.0b013e3181e37884.
21 Iannetta D, De Maria M, Bolletta E, Mastrofilippo V, Moramarco A, Fontana L. Subretinal injection of recombinant tissue plasminogen activator and gas tamponade to displace acute submacular haemorrhages secondary to age-related macular degeneration. OPTH. 2021;15:3649–59. https://doi.org/10.2147/OPTH.S324091.
22 Iglicki M, Khoury M, Donato L, Quispe DJ, Negri HP, Melamud JI. Comparison of subretinal aflibercept vs ranibizumab vs bevacizumab in the context of PPV, pneumatic displacement with subretinal air and subretinal tPA in naïve submacular haemorrhage secondary to nAMD. "The Submarine Study". Eye. 2024;38(2):292–6. https://doi.org/10.1038/s41433-023-02676-9.
23 Iglicki M, Khoury M, Melamud JI, Donato L, Barak A, Quispe DJ, et al. Naïve subretinal haemorrhage due to neovascular age-related macular degeneration. pneumatic displacement, subretinal air, and tissue plasminogen activator: subretinal vs intravitreal aflibercept-the native study. Eye. 2023;37(8):1659–64. https://doi.org/10.1038/s41433-022-02222-z.

24 Kitagawa Y, Shimada H, Mori R, Tanaka K, Wakatsuki Y, Onoe H, et al. One-year outcome of intravitreal tissue plasminogen activator, ranibizumab, and gas injections for submacular hemorrhage in polypoidal choroidal vasculopathy. J Clin Med. 2022;11(8):2175. https://doi.org/10.3390/jcm11082175.
25 Kumar A, Roy S, Bansal M, Tinwala S, Aron N, Temkar S, et al. Modified approach in management of submacular hemorrhage secondary to wet age-related macular degeneration. Asia Pac J Ophthalmol. 2016;5(2):143–6. https://doi.org/10.1097/APO.0000000000000130.
26 Limon U, Gezginaslan TA, Saygin IO, Bozkurt E, Kardes E, Akcay BIS. Efficacy of simultaneous application of subretinal tissue plasminogen activator and bevacizumab for submacular hemorrhages. Beyoglu Eye J. 2023;8(3):198–207. https://doi.org/10.14744/bej.2023.34735.
27 Lee JP, Park JS, Kwon OW, You YS, Kim SH. Management of acute submacular hemorrhage with intravitreal injection of tenecteplase, anti-vascular endothelial growth factor and gas. Korean J Ophthalmol. 2016;30(3):192–7. https://doi.org/10.3341/kjo.2016.30.3.192.
28 Ogata M, Oh H, Nakata A, Doi A, Nakayama H, Hasegawa M, et al. Displacement of submacular hemorrhage secondary to age-related macular degeneration with subretinal injection of air and tissue plasminogen activator. Sci Rep. 2022;12(1):22139. https://doi.org/10.1038/s41598-022-26289-6.
29 Patikulsila D, Winaikosol P, Choovuthayakorn J, Watanachai N, Chaikitmongkol V, Kunavisarut P. Pars plana vitrectomy and subretinal tissue plasminogen activator for large exudative submacular hemorrhage: a case series. BMC Ophthalmol. 2022;22(1):411. https://doi.org/10.1186/s12886-022-02639-w.
30 Ramesh A, Ramanjulu R, Shanmugam M, Chaitanya V. Not-so-minimal for minimally invasive surgery. Indian J Ophthalmol. 2022;70(2):665–6. https://doi.org/10.4103/ijo.IJO_1726_21.
31 Rickmann A, Paez LR, Della Volpe Waizel M, Bisorca-Gassendorf L, Schulz A, Vandebroek AC, et al. Functional and structural outcome after vitrectomy combined with subretinal rtPA Injection with or without additional intravitreal Bevacizumab injection for submacular hemorrhages. PLoS One. 2021;16(4):e0250587. https://doi.org/10.1371/journal.pone.0250587.
32 Treumer F, Klatt C, Roider J, Hillenkamp J. Subretinal coapplication of recombinant tissue plasminogen activator and bevacizumab for neovascular age-related macular degeneration with submacular haemorrhage. Br J Ophthalmol. 2010;94(1):48–53. https://doi.org/10.1136/bjo.2009.164707.
33 Vision Academy Steering Committee [internet]. Vision Academy viewpoint: management of subfoveal hemorrhage. [cited 2023 Nov 17]. Available from: https://www.visionacademy.org/sites/g/files/vrxlpx7586/files/2021-06/Management-of-subfoveal-hemorrhage-Viewpoint.pdf.
34 Jackson TL, Bunce C, Desai R, Hillenkamp J, Lee CN, Lois N, 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. https://doi.org/10.1186/s13063-021-05966-3.