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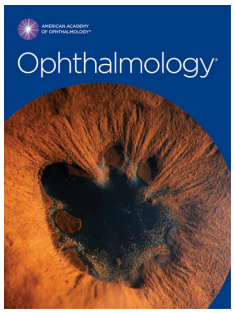

STAR: a randomized controlled trial for submacular hemorrhage secondary to age-related macular degeneration

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STAR: a randomized controlled trial for submacular hemorrhage secondary to age-related macular degeneration

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Conflict of interest summary

The authors indicate no financial support specifically for this study. P-H. Gabrielle has received travel expenses from AbbVie, Bayer and Novartis and is a medical consultant for Novartis, Horus pharma and Bayer. A Glacet-Bernard is a medical consultant for Novartis and Bayer. M-N Delyfer has received travel expenses from AbbVie, Bayer and Novartis and is medical consultant for AbbVie, Bayer, Horus Pharma, Novartis, Roche and Théa. JB Conart has received travel expenses from Bayer and Novartis and is a medical consultant for Roche, Novartis, Hoya and Bayer. J Uzzan has received personal fees from Bayer. L Kodjikian is a medical consultant for AbbVie, Bayer, Alimera, Horus Pharma, Krys,

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Running head/short title (max 60 characters): Surgery vs. pneumatic displacement for SMH

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Abbreviations

AMD	Age-related macular degeneration
VEGF	Vascular endothelial growth factor inhibitor
BCVA	Best-corrected visual acuity
CNIL	Commission Nationale de l'Informatique et des Libertés
CPP	Comité de Protection des Personnes
DD	Disk diameter
ETDRS	Early Treatment Diabetic Retinopathy Study
FRB!	Fight retinal blindness!
INR	International normalized ratio
IVT	Intravitreal injection
PD	Pneumatic displacement
PPV	Pars plana vitrectomy
PROM	Patient-reported outcome measure
QoL	Quality of life
RCT	Randomized controlled trial
RPE	Retinal pigment epithelium
SD-OCT	Spectral Domain Optical Coherence Tomography
SF6	Sulfahexafluoride
SMH	Submacular hemorrhage
STAR	Surgery, Tissue plasminogen ActivatoR

tPA	Tissue plasminogen activator
VA	Visual acuity
VFQ-25	National Eye Institute 25-item Visual Function Questionnaire

Abstract (375 words)

Objective: To compare the efficacy and the safety of submacular hemorrhage (SMH) management with either surgical *pars plana* vitrectomy (PPV) or pneumatic displacement (PD), with tissue plasminogen activator (TPA) and vascular endothelial growth factor (VEGF) inhibitor added to each arm.

Design: Randomized, open-label, multicenter superiority study.

Participants: Ninety patients with neovascular age-related macular degeneration (nAMD) aged ≥50 years, with recent SMH (≤14 days) greater than 2 optic disk areas and predominantly overlying the retinal pigment epithelium.

Interventions: Patients were randomly assigned to surgery (PPV, subretinal TPA [max 0.5 ml/50 μg], and 20% sulfahexafluoride [SF6] tamponade) or PD (0.05 ml intravitreal TPA [50 μg] and 0.3 ml intravitreal pure SF6). Both groups were asked to maintain a head upright position with the face forward at 45° for 3 days after intervention and received 0.5 mg intravitreal ranibizumab at the end of the intervention, at Month 1 and 2, as the loading phase, and then on a *pro re nata* regimen during a 6-month follow-up.

Methods and outcome measures: The primary efficacy endpoint was mean best-corrected visual acuity (VA) change at Month 3. The secondary endpoints were mean VA change at Month 6, National Eye Institute 25-item Visual Function Questionnaire (VFQ-25) composite score value at Month 3 and 6, number of anti-VEGF injections, and complications during the 6-month follow-up.

Results: Of the 90 patients randomized, 78 (86.7%) completed the 3-month efficacy endpoint visit. The mean±SD age was 83.3±8.2 years, and 66.3% were female. The mean duration of symptoms before treatment was 7.5±4.4 days. The mean VA change from baseline to Month

3 in the surgery group (+16.8 letters, [95% CI, 8.7; 24.9]) was not significantly superior to the PD group (+16.4 letters, [95% CI, 7.1;25.7]; adjusted difference β, -1.9 [95% CI, -14.9;11.0], $P = 0.767$). Both groups achieved similar secondary outcomes at Month 6. No unexpected ocular safety concerns were observed in either group.

Conclusions: Surgery did not yield superior visual gain nor additional benefit for SMH secondary to nAMD compared to PD at 3 months, with intravitreal anti-VEGF added to each arm. Both treatment strategies lead to a clinical improvement of visual acuity without safety concerns for SMH over 6 months. Both design and results of the trial cannot be used to establish equivalence between treatments.

Introduction

Submacular hemorrhage (SMH) is an acute and rare sight-threatening complication characterized by an accumulation of blood under the retina arising from the choroidal or retinal circulation. The most common cause of SMH is neovascular age-related macular degeneration (nAMD).[1] The incidence of SMH was recently estimated to be 0.46% in a 10-year observational study of 7642 eyes (6425 patients) treated with vascular endothelial growth factor (VEGF) inhibitors for nAMD in daily practice.[2] Patients with SMH usually have sudden severe vision loss with visual acuity (VA), often lower than 20/200. SMH may occur as the first manifestation of nAMD, and good VA in the fellow eye can lead to a delay in patient management with adverse consequences,[3] since treatment delay is a key prognostic factor for SMH outcomes.[4, 5]

SMH treatment strategies aim to clear blood away from the macula and prevent further bleeding.[5] Clinical evidence supporting the various therapeutic options is mostly limited to case series. There is only one large randomized controlled comparative trial (RCT) reported to date , the Submacular Surgery Trial (SST), which was published before the VEGF inhibitor era and compared the surgical approach to observation but did not demonstrate improvement or stabilization of VA.[6] Surgery usually involves *pars plana* vitrectomy (PPV) with subretinal injection of the thrombolytic serine protease recombinant-tissue plasminogen activator (tPA) to liquefy the clot, with subsequent air or gas tamponade, aiding dispersal and resorption of blood from the macula. Less invasive SMH treatment strategies have been proposed with intravitreal injection (IVT) of expansile gas, often sulfahexafluoride (SF6), to pneumatically displace the clot and can be combined with intravitreal injection of tPA.[7] These therapeutic options have been associated with anti-VEGF IVT since their approval for nAMD, even though pivotal RCTs excluded patients with SMH. Indeed, the addition of anti-VEGF treatment has

the advantage of also treating the underlying AMD.[3] The pneumatic displacement (PD) strategy, combined with intravitreal tPA and anti-VEGF injection, offers several advantages: it is easy to perform, inexpensive, and minimally invasive (which is an important advantage in the elderly population with AMD). However, surgical management with vitrectomy remains popular, especially in large SMH. There is currently a lack of evidence from RCTs, with variable reporting of outcomes and poor characterization of SMH at presentation.[8] Treatment guidelines acknowledge the lack of high-quality evidence and do not provide clear treatment recommendations.[9]

The purpose of this prospective randomized controlled clinical trial, STAR (Surgery, Tissue plasminogen ActivatoR, antiangiogenic agents and age-related macular degeneration), was to evaluate the safety and efficacy of surgical treatment (i.e. PPV, subretinal tPA and 20% SF6) compared to PD (i.e. intravitreal tPA and SF6) combined with anti-VEGF IVT for SMH secondary to nAMD.

Methods

Study design

We hypothesized that surgical treatment would have superior visual outcomes (a two-line improvement in vision) than PD with an acceptable safety profile. This was a prospective, randomized, multicenter, open-label superiority trial in patients with nAMD, comparing the visual outcomes and safety of SMH management via surgery (PPV plus subretinal tPA, SF6 tamponade) or PD (intravitreal SF6 plus tPA). In addition, an intravitreal injection with 0.5mg ranibizumab (0.5 mg Lucentis, Genetech Inc/Novartis) was performed at the end of the procedure in both groups.

STAR was funded by the French national research program "Programme Hospitalier Recherche Clinique" with Dijon University Hospital as the sponsor. STAR was approved by the institutional review boards (French ethics committee [CPP] and the French data protection agency [CNIL]), complied with the ethical standards defined by the Declaration of Helsinki and Good Clinical practice, and was registered on Clinicaltrials.gov (NCT02557451). An independent data and safety monitoring board reviewed safety data. All patients provided informed consent before participating in the study. Potential patients were provided with information at selection visit. Patients who agreed to participate then attended the enrolment visit for baseline assessments and randomization, and were subsequently treated according to the randomized treatment strategy (surgery or PD). All visual outcomes and safety were assessed monthly up to Month 6. There were no major changes to the study design after the study started. Overall, 90 patients were enrolled from 13 hospitals in France between 28 April 2016 and 28 October 2019, with the last patient's final visit on 5 May 2020.

Eligibility criteria

Eligible patients were aged at least 50 years and presented with visual loss due to a recent SMH (first symptoms ≤14 days prior to treatment) secondary to nAMD, with 1) the presence of blood predominantly overlying the retinal pigment epithelium (RPE) with a minimum thickness above 100µm assessed through spectral domain optical coherence tomography (SD-OCT) and its manual caliper function and 2) SMH diameter greater than two optic disk diameters (DD) on retinal photographs. Only one eye per patient was included.

Patients were excluded if they had any of the following: SMH linked to a cause other than AMD (such as myopia, angioid streaks, or arterial macroaneurysm), history of SMH in the same eye, presence of macular scar, patient presenting >14 days after the onset of visual loss, sub-RPE hemorrhage exclusively, thin hemorrhage without retinal elevation (maximum

thickness of the clot <100 µm on SD-OCT), international normalized ratio (INR) for coagulation >4 (contraindicating surgery), need for cataract surgery within the first 3 months of study.

Randomization

At the inclusion visit, investigators used the secure Tenalea™ internet-based software (Formsvision BV, Abcoude, Netherlands) to randomize eligible patients in a 1:1 ratio to receive either surgical or PD treatment. The allocation algorithm was determined by the statistician of the coordination center before the start of the trial (Clinical Investigation Centre - Clinical Epidemiology/ Clinical Trials (CIC-EC), Dijon, France). The allocation was based on a minimization approach considering nAMD pretreated status (yes versus no) and center. Due to the nature of the study intervention, it was impossible to mask patients or investigators to the assignment of the intervention. However, VA measurements and imaging assessments were performed by an independent blinded orthoptist and investigator at each site throughout the study, respectively.

Treatment

Both groups of participants were treated by senior vitreoretinal surgeons in the operating room of participating sites. Participants randomized to the surgery group were treated under local anesthesia. The procedure involved a complete transconjunctival PPV, with posterior vitreous detachment if the vitreous was still attached. Then, alteplase tPA (Actilyse®, Boehringer Ingelheim, France; with a diluted concentration of 100 µg in 1 ml) was injected into the superior margin of the SMH to create a local retinal detachment using a cannula with a retractable 41G tip (Dutch Ophthalmic Research [DORC], Zuidland, The Netherlands). The volume required depended on the amount needed to cover the SMH, with a maximum injected volume of 0.5 ml (50 µg). The peripheral retina was then checked carefully for retinal tears which were

treated, if present, with laser or cryotherapy as clinically indicated. A complete fluid-air exchange was performed, followed by an air-gas exchange of 20% SF6 using at least 30 ml of diluted gas. Finally, 0.05 ml (0.5 mg) of ranibizumab was injected intravitreally at the end of the procedure. The patient was asked to maintain the head upright with the face forward at 45° for 3 days after surgery.

Participants randomized to the PD group were treated under topical anesthesia. First, 0.05 ml (50 μg) of alteplase tPA (Actilyse®, Boehringer Ingelheim, France; with a concentration of 1000 μg in 1 ml) was injected intravitreally using a 30-gauge needle. Then, 0.05 ml (0.5 mg) of ranibizumab was injected intravitreally, followed by an anterior chamber paracentesis of 0.3 to 0.5 ml. Finally, 0.3 ml of pure SF6 gas was injected. All injections were administered via the pars plana 3.0 mm posterior to the limbus in pseudophakic participants and 3.5 mm posterior to the limbus in phakic participants. The patient was asked to maintain the head upright with the face forward at 45° for 3 days after the procedure.

Participants in the surgery group were treated postoperatively with topical corticosteroids, intraocular pressure-lowering drugs, and antibiotics for 4 weeks. Participants in the PD group were treated with intraocular pressure-lowering drug for 5 days after injection. Participants in each treatment group also received intravitreal ranibizumab injections, administered at Month 1 and 2 as the loading phase. Additional injections at Months 3, 4, 5, and 6 were administered at the blinded investigator's discretion according to the presence of hemorrhage and/or sign of active choroidal neovascular lesion on multimodal imaging (subretinal and/or intra-retinal fluid).

Assessments

The following assessments were performed at each visit (enrolment visit up to Month 6) except the day of treatment (Day 0): best-corrected VA using the Early Treatment Diabetic

Retinopathy Study (ETDRS) standard scale[10], SD-OCT examination (Spectralis Heidelberg Engineering GmbH, Heidelberg, Germany), and color fundus retinal photography centered on the macula. Visual acuity was measured as a continuous letter score from 100 to 1, with higher numbers indicating better VA. For participants with reduced vision at 4 meters, testing distance was reduced to 1 meter. If VA was less than 20/800, a conversion was used: "No perception of light" was 0 letter, "perceive light" was 1 letter, "hand movement" was 2 letters and "count fingers" was 3 letters read. VA was assessed by a blinded experienced orthoptist at each site with certified equipment. Multimodal imaging was acquired and graded by an independent centralized blinded trial investigator. Fluorescein and indocyanine green angiographies were recommended but performed at the investigator's discretion.

The area of SMH was measured as the largest diameter measured on color fundus photography to define three groups (i.e. <2 DD, 2-5 DD or >5 DD). SMH thickness was measured on SD-OCT imaging using the OCT manual caliper function as the maximum hemorrhage thickness, defined as the distance between the inner limiting membrane and RPE, when RPE could be identified. At enrolment, Month 3 and Month 6, quality of life was assessed using the validated patient-reported outcome Visual Function Questionnaire (National Eye Institute 25-item Visual Function Questionnaire [VFQ-25]).[11]

Adverse events were recorded at every visit from the treatment day (Day 0) to Month 6. Serious adverse events were declared to the trial vigilance unit and categorized according to the classification Medical Dictionary for Regulatory Activities (MedDRA version #25.1). The trial vigilance unit defined the causality in case of a serious adverse event. Furthermore, an independent data and safety monitoring board (DSMB) periodically reviewed safety data during the trial.

There were no changes to the trial outcomes after the study start.

Statistical analyses

Population size

STAR was a superiority trial. The sample size was based on the primary outcome, VA change from baseline (enrolment) to Month 3. Assuming mean VA gains of 10 letters (±10) letters in the surgery group and 5 letters (±5 letters) in the PD group, 82 participants (41 per group) were needed to detect superior VA gain in the surgery group with a power of 80% and a two-sided significant level of 0.05.[12-14] To control for the risk of attrition, it was planned to include 90 participants (45 per group).

Endpoints

The primary endpoint was the mean change in VA from baseline to Month 3. Secondary efficacy endpoints were: VA change at Month 6, VFQ-25 composite score value at Months 3 and 6, and the number of anti-VEGF injections at Month 6. Endpoints associated with safety were: the number of participants with at least one episode of recurrence by Month 6, and the rate of complications by Month 6.

Statistics

The main analysis was performed according to the intent-to-treat principle and included all randomized participants. Categorical variables are expressed as numbers and percentages. Continuous variables are presented as means and standard deviation or medians and interquartile ranges, as appropriate. VA change from baseline to Month 3 (primary outcome) was compared between groups using Student-t test (univariate analysis) followed by a multiple linear regression adjusted on randomization stratification factors (nAMD pretreated status [pretreated or naive nAMD] and center). Comparisons of secondary outcomes were made using standard univariate tests followed by use of multiple regression (logistic or linear multiple regression). The statistical analysis plan did not consider that secondary analyses would be

corrected for multiple comparisons. As such the 95% confidence intervals were not adjusted for multiplicity and should not be used to infer definitive conclusions on treatment effect for secondary outcomes. Safety was evaluated by calculating the percentages of participants in the two groups with complications and adverse events, particularly retinal detachment, vitreous hemorrhage, and cataract. A per protocol analysis (using the same techniques as the intent-to-treat analysis) excluded participants not receiving anti-VEGF injections at Month 1 and/or Month 2 and those who did not complete the Month 3 visit. Primary outcome analysis was completed with sensitivity analyses. A first analysis was conducted using a multiple linear regression adjusted on randomization stratification factors and imbalanced baseline covariates. A second analysis was carried out using multiple imputations by fully conditional specification to impute missing VA at Month 3. Imputation for VA change to Month 3 was based on treatment allocation, baseline VA, age, gender, pretreated AMD status, and center. No interim analyses were planned or performed. Finally, for exploration purposes, we performed a *post-hoc* subgroup analysis of visual outcomes according to SMH diameter and thickness.

Analyses were performed with SAS software 9.4 (SAS Institute, Care, USA). All tests were two sided with a $P < 0.05$ significance level. The main conclusion of the trial was based on the intent-to-treat analysis.

Results

Participants

In total, 90 patients were randomized, 89 patients were treated, 78 (87.6%) patients completed the Month 3 visit and 72 (80.9%) patients completed the Month 6 visit (Figure 1). The intent-to-treat analysis population included 40 patients in the surgery group and 38 patients in the PD group at Month 3 (Figure 1). The overall mean±SD age was 83.3±8.2 years, and 66.3 % were female. Almost one-third of our patients were treated with anticoagulant or antiplatelet agents.

69.7 % of patients had AMD in the contralateral eye, but 26.6% had no history of AMD (Table 1). There were more females in the surgery group than in the PD group (73.3% versus 59.1%). The mean baseline VFQ-25 composite score was lower in the surgery group than in the PD group (53.9±20.0 versus 64.6±22.1). Otherwise, treatment groups were well balanced in terms of demographics, comorbidities and AMD disease characteristics and prior treatments (Table 1). The median time from SMH onset to treatment was 6.5 days (range: 4.0-10.0) in the surgery group and 7.0 days (range: 3.0-11.0) in the PD group. Patient baseline characteristics are presented by completion of the Month 3 visit in Table S2 (available at http://www.aaojournal.org), with no significant differences between those who did and did not complete the Month 3 visit. Baseline visual and SMH imaging characteristics were similar between both groups (Table 3), although the surgery group had somewhat more patients with large SMH (diameter >5 DD) (43.9% versus 27.5% in the PD group) and thicker SMH (1098 ± 585μm versus 966 ± 330μm in the PD group) (Table 3). Most patients (83.1%) had SMH with both subretinal and RPE involvement.

Efficacy

The mean change in VA improved up to Month 1 and then stabilized to Month 6 in both groups (Figure 2). The mean VA change from baseline to Month 3 was 16.8 letters (95% CI: 8.7;24.9) in the surgery group and 16.4 letters (95% CI: 7.1;25.7) in the PD group. No significant difference between treatment groups was observed in VA change to Month 3 (adjusted β 1.9 [95% CI: -11.0; 14.9], p=0.767) (Table 4). Similar results were observed in the per protocol analysis (adjusted β 1.8 [95% CI: -11.3; 14.9], P = 0.787) (Table S5 and Figure S3, available at http://www.aaojournal.org) and in the sensitivity analyses (Table S6, available at http://www.aaojournal.org). After adjusting for baseline SMH imbalanced characteristics, such as SMH diameter and thickness, there was no significant difference in VA change between groups (adjusted β 2.0 [95% CI: -11.4; 13.5], P = 0.767) (Table S6 and S7, available at

http://www.aaojournal.org). No significant differences were identified between groups for secondary endpoints (Table 4). At Month 6, the mean VA letter score improvement was 17.2 letters (95% CI: 9.1;25.4) in the surgery group and 15.4 letters (95% CI: 5.7;25.1) in the PD group, with no difference between groups (adjusted β 3.3 [95% CI: -10.5; 17.0], P = 0.776) (Table 4). The percentage of eyes with VA gain or worsening by ≥10- or ≥15-letters remained similar between groups throughout the study (Figures S4 to S7, available at http://www.aaojournal.org). Overall, VFQ-25 composite score value remained stable from baseline to Month 3 and Month 6. There was no meaningful difference in the VFQ-25 composite score value at Month 3 and Month 6 between groups (Table 4). VFQ-25 domain score data are provided in Table S8 and S9 (available at http://www.aaojournal.org).

Additional anti-VEGF injections between Month 3 and Month 6 were administered to 73.3% of patients in the surgery group and 84.1% in the PD group, with no statistically significant differences between treatment groups. The median (IQR) number of injections over 6 months was similar between treatment groups (4.0 [3.0; 4.0] in the surgery group vs. 3.0 [2.0; 4.0] in the PD group, adjusted β 0.1 [95% CI: -0.1; 0.4], P = 0.334) (Table 4).

Safety

Overall 12 (26.7%) patients in the surgery group had 18 ocular adverse events and 12 (27.3%) patients in the PD group had 16 ocular adverse events (Table 10). Three ocular adverse events were reported as serious, of which none were related to the treatment (Table S11, available at http://www.aaojournal.org). One patient died during the study for a reason unrelated to the treatment. Two patients withdrew from the study due to adverse events; one due to retinal detachment and one due to SMH recurrence. Endophthalmitis did not occur in either group. There were four events of retinal detachment (two per operative and two post operative) in the surgery group. There were two events of recurrence in the surgery group and six in the PD

group. All systemic adverse events and ocular adverse of the non-study eye are reported in the Table S12 (available at http://www.aaojournal.org).

Discussion

The STAR study is the largest RCT comparing treatment options for SMH with subretinal component in the anti-VEGF agent era. Our 6-month superiority trial compared the effectiveness and safety of treatment with surgery or PD in a homogeneous population of patients with SMH secondary to nAMD. We showed that both treatment modalities lead to a clinical improvement of visual acuity at Month 3 of approximately three lines in each group. However, surgery did not provide a superior visual gain than PD at Month 3, nor at Month 6. This superiority study was not designed to establish equivalence between treatment modalities. The 95% confidence interval of the difference between groups includes meaningful differences in visual acuity. Thus, both design and results of the STAR study cannot be used to establish equivalence between surgery and PD.

The higher visual outcomes in our study compared to the SST trial carried out before the approval of anti-VEGF IVT emphasize that anti-VEGF agents have dramatically improved outcomes of nAMD and its complications. The demographics of patients in the STAR trial reflected the populations described in recent studies of SMH epidemiology[2] and treatments.[7, 15-17] We found similar outcomes with the first pilot RCT published in the era of VEGF inhibitor without significant difference between surgery versus PD, though this feasibility trial had a smaller sample size.[18] A retrospective study[16] and a 38-study review[18] also reported comparable outcomes with surgery versus PD. A registry study reported that both strategies resulted in improved SMH and/or visual outcomes, without comparing the magnitude of improvements in each group.[2] Unlike STAR, these studies were not sized enough or not randomized, controlled nor prospective. These retrospective studies also used heterogenous surgical procedures, in terms of the technique and gauge of the tip to inject

subretinal tPA, the type of gas used for tamponade or the type and duration of the postoperative position.[19]

Factors influencing the choice of treatment strategy for SMH include the size, thickness, duration and location of the bleeding (above or under the RPE).[20] Neither surgery nor PD is recommended in the management of sub-RPE bleeding and should only be considered for hemorrhages that are predominantly subretinal, as reflected in STAR's eligibility criteria. Previous studies suggested that anti-VEGF monotherapy may be sufficient for small SMH,[7, 13, 21-24] and that vitrectomy might be superior in the case of thickened or extensive SMH.[7, 15, 17] Despite randomization, surgery-treated patients tended to have larger and thicker SMH at baseline than PD-treated patients in our study. After adjustment for those imbalanced baseline characteristics in the sensitivity analysis, there was no significant difference in VA change between both groups. Furthermore, even though the STAR study design was not powered enough, *post hoc* subgroup analyses confirmed that there was no visual superiority of one modality over the other depending on the size and thickness of SMH at baseline (Table S7, available at http://www.aaojournal.org).

Clinical measures such as visual acuity do not capture the influence of eye diseases and their treatments on patients' visual function, psychological stress, well-being and quality-of-life,[25] which can be evaluated using patient-reported outcome measures (PROMS), such as VFQ-25 score, that capture the patient's disease angle of view. PROMS are becoming more widely used to comprehensively report the impact of disease and treatment effectiveness on patients, since regulatory agencies recommend using PROMS.[26, 27] Unfortunately, neither treatment modality appeared to significantly improve the overall quality-of-life of SMH patients over 6 months. The PROMS have not been reported by any previous study assessing SMH treatments since anti-VEGF IVT has been approved for nAMD.

The average number of optional anti-VEGF injections from Month 3 to Month 6, administered in a *pro re nata* regimen, was similar between the surgery and PD groups (3.2 and 2.8 injections, respectively). Similar numbers of injections have been reported in other studies of equal duration.[16, 28] This finding highlights that the choroidal neovascularization lesion in SMH patients remains active for several months, requiring several anti-VEGF injections, whatever the procedure used to treat SMH.

Both treatment modalities had good safety profiles, with around a quarter of patients in each group having at least one adverse ocular event related to the treatment. These complications were well known risks linked to surgery or pneumatic displacement. The rate of SMH recurrence tended to be more frequent in the PD group (n=6 [4.4%] versus n=2 [13.6%] in the surgery group), while more retinal detachments occurred in the surgery group (n=4 [8.8%] versus n=0 in the PD group), in line with previously reported rates for those complications.[4, 5, 17, 29]

Surgical treatment is costly (average cost of $2500 only for the procedure), time-consuming, and must be performed in the operating theatre using specialized equipment and a team of trained ophthalmologists and nurses. Our results suggest that the less invasive PD approach can be considered unless specific parameters indicate otherwise. Selection of a treatment strategy may also be limited by national or local reimbursement of anti-VEGF agents, which are not systematically indicated or reimbursed when VA is very low. The VA improvement in both groups highlights the importance of promptly treating SMH, whatever treatment strategy is chosen, given that VA outcomes are poor without any treatment.[30] Results from STAR will help address the comparative evidence gap, which has thus far prevented the establishment of a clear management consensus for SMH.[3, 9]

We acknowledge several limitations. First, a double-blind study design was not possible due to the nature of the treatment arms. However, the blinded outcome assessment mitigated this weakness during the trial. Secondly, despite previous studies demonstrating effectiveness in some SMH, we did not include an anti-VEGF monotherapy arm.[2, 13, 21-24] This was because we excluded patients with SMH <2 DD and exclusively sub-RPE involvement. These excluded patients are good candidates for anti-VEGF monotherapy. Furthermore, adding a VEGF inhibitor monotherapy arm would have significantly inflated the trial's sample size, which would have been difficult to reach even as a multicenter national study since SMH remains a relatively rare complication in nAMD.[2] The ongoing randomized prospective TIGER trial, assessing anti-VEGF (aflibercept) monotherapy versus surgery (PPV, subretinal tPA, 20% SF6 gas tamponade and aflibercept) for SMH, should elucidate the place of anti-VEGF monotherapy in the therapeutic arsenal.[31] Thirdly, another limit was the relatively short 6-month follow-up, with the primary endpoint reported at Month 3. However, other studies showed that VA at Month 3 is strongly correlated with VA at Month 12.[7, 15] A follow-up longer than 6 months would also have led to difficulties distinguishing the impact on VA from SMH treatment and AMD treatment. Finally, some baseline characteristics were not similar between groups, including some that might influence the primary outcome such as SMH size. However, statistical adjustment for those differences and a post hoc subgroup analysis did not materially alter our main results.

This study had several strengths, including a substantial population size given the rarity of SMH without high attrition rate at the primary endpoint, the randomized controlled study design with outcome assessors who were blinded to treatment assignment, the inclusion of quality-of-life measures and the use of SD-OCT to exclude patients unlikely to benefit from the study treatments, due to predominantly sub-RPE hemorrhage.

In conclusion, the STAR trial is the largest RCT investigating SMH treatment options in the era of VEGF inhibitors. Our study did not show surgery to be superior to PD regarding visual gain, quality-of-life, and post-treatment anti-VEGF use. Our trial design and data cannot be used to establish equivalence between treatments. Hence, a larger clinical trial designed for equivalence would be necessary. Both treatment strategies lead to a clinical improvement of visual acuity without safety concerns for SMH over 6 months. SMH should be treated promptly, and the treatment strategy should be selected based on the patient's comorbidities, treatment and SMH characteristics, and the ophthalmologist's expertise and experience.

References

1. Avery RL, Fekrat S, Hawkins BS, Bressler NM. Natural history of subfoveal subretinal hemorrhage in age-related macular degeneration. Retina 1996;16(3):183-9.

2. Gabrielle PH, Maitrias S, Nguyen V, et al. Incidence, risk factors and outcomes of submacular haemorrhage with loss of vision in neovascular age-related macular degeneration in daily clinical practice: data from the FRB! registry. Acta Ophthalmol 2022.

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.

4. Iannetta D, De Maria M, Bolletta E, et al. Subretinal Injection of Recombinant Tissue Plasminogen Activator and Gas Tamponade to Displace Acute Submacular Haemorrhages Secondary to Age-Related Macular Degeneration. Clin Ophthalmol 2021;15:3649-59.

5. González-López JJ, McGowan G, Chapman E, Yorston D. 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):929-35.

6. Bressler NM, Bressler SB, Childs AL, et al. Surgery for hemorrhagic choroidal neovascular lesions of age-related macular degeneration: ophthalmic findings: SST report no. 13. Ophthalmology 2004;111(11):1993-2006.

7. Jeong S, Park DG, Sagong M. Management of a Submacular Hemorrhage Secondary to Age-Related Macular Degeneration: A Comparison of Three Treatment Modalities. J Clin Med 2020;9(10).

8. Al-Hity A, Steel DH, Yorston D, et al. Incidence of submacular haemorrhage (SMH) in Scotland: a Scottish Ophthalmic Surveillance Unit (SOSU) study. Eye (Lond) 2019;33(3):486-91.

9. Schmidt-Erfurth U, Chong V, Loewenstein A, et al. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). Br J Ophthalmol 2014;98(9):1144-67.

10. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol 1985;103(12):1796-806.

11. Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2001;119(7):1050-8.

12. Kauffmann Y, Isaico R, Lefebvre A, et al. [Relationship between intravitreal anti-VEGF therapy and subretinal hemorrhage in patients with exudative age-related macular degeneration]. J Fr Ophtalmol 2014;37(3):195-201.

13. McKibbin M, Papastefanou V, Matthews B, et al. Ranibizumab monotherapy for sub-foveal haemorrhage secondary to choroidal neovascularisation in age-related macular degeneration. Eye (Lond) 2010;24(6):994-8.

14. Sandhu SS, Manvikar S, Steel DH. Displacement of submacular hemorrhage associated with age-related macular degeneration using vitrectomy and submacular tPA injection followed by intravitreal ranibizumab. Clin Ophthalmol 2010;4:637-42.

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 rtPA and anti-VEGF. Graefes Arch Clin Exp Ophthalmol 2017;255(6):1115-23.

16. Grohmann C, Dimopoulos S, Bartz-Schmidt KU, et al. Surgical management of submacular hemorrhage due to n-AMD: a comparison of three surgical methods. Int J Retina Vitreous 2020;6:27.

17. Pierre M, Mainguy A, Chatziralli I, et al. Macular Hemorrhage Due to Age-Related Macular Degeneration or Retinal Arterial Macroaneurysm: Predictive Factors of Surgical Outcome. J Clin Med 2021;10(24).

18. van Zeeburg EJ, van Meurs JC. Literature review of recombinant tissue plasminogen activator used for recent-onset submacular hemorrhage displacement in age-related macular degeneration. Ophthalmologica 2013;229(1):1-14.

19. Kadonosono K, Arakawa A, Yamane S, et al. Displacement of submacular hemorrhages in age-related macular degeneration with subretinal tissue plasminogen activator and air. Ophthalmology 2015;122(1):123-8.

20. Bopp S, Mirshahi A. Classification of Macular Hemorrhages. In: LO H, ed. Management of Macular Hemorrhage: Springer, 2018.

21. Stifter E, Michels S, Prager F, et al. Intravitreal bevacizumab therapy for neovascular age-related macular degeneration with large submacular hemorrhage. Am J Ophthalmol 2007;144(6):886-92.

22. Chang MA, Do DV, Bressler SB, et al. Prospective one-year study of ranibizumab for predominantly hemorrhagic choroidal neovascular lesions in age-related macular degeneration. Retina 2010;30(8):1171-6.

23. Shienbaum G, Garcia Filho CA, Flynn HW, Jr., et al. 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.

24. Kim JH, Chang YS, Kim JW, et al. Intravitreal anti-vascular endothelial growth factor for submacular hemorrhage from choroidal neovascularization. Ophthalmology 2014;121(4):926-35.

25. Massof RW. The measurement of vision disability. Optom Vis Sci 2002;79(8):516-52.

26. Fehnel S, DeMuro C, McLeod L, et al. US FDA patient-reported outcome guidance: great expectations and unintended consequences. Expert Rev Pharmacoecon Outcomes Res 2013;13(4):441-6.

27. Pesudovs K. Patient-centred measurement in ophthalmology--a paradigm shift. BMC Ophthalmol 2006;6:25.

28. Avcı R, Mavi Yıldız A, Çınar E, 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.

29. Ben Ghezala I, Mariet AS, Benzenine E, et al. Incidence of rhegmatogenous retinal detachment following macular surgery in France between 2006 and 2016. Am J Ophthalmol 2022.

30. Childs AL, Bressler NM, Bass EB, et al. Surgery for hemorrhagic choroidal neovascular lesions of age-related macular degeneration: quality-of-life findings: SST report no. 14. Ophthalmology 2004;111(11):2007-14.

31. 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.

Figure legends

Figure 1. Flowchart of participants.

Figure 2. Mean (95% CI) change in visual acuity from baseline over the study period. The black spot represents the mean, and the upper and lower whisker extends to the superior and inferior value of the 95% confidence interval.

Table 1. Participants' characteristics, at enrolment visit

Characteristic	Overall n=89	Surgery group n=45	Pneumatic displacement group n=44
Female, n (%)	59 (66.3)	33 (73.3)	26 (59.1)
Age, years, mean±SD	83.3±8.2	84.3±8.3	82.29±8.0
Treatment, n (%)			
None	38 (42.7)	17 (37.8)	21 (47.7)
Anticoagulant alone	22 (24.7)	14 (31.1)	8 (18.2)
Antiplatelet agent alone	28 (31.5)	14 (31.1)	14 (31.8)
Anticoagulant and antiplatelet agents	1 (1.1)	0	1 (2.3)
Comorbidities, n (%)			
Systemic arterial hypertension	58 (65.9)	28 (62.2)	30 (69.8)
History of stroke	5 (5.6)	2 (4.4)	3 (6.8)
History of myocardial infarction	8 (9.0)	4 (8.9)	4 (9.1)
Years since AMD diagnosis,[a] mean±SD	2.9±3.0	3.3±3.2	2.5±2.7
Lens status, n (%)	31 (34.8)	15 (33.3)	16 (36.4)
AMD in contralateral eye, n (%)	62 (69.7)	30 (66.7)	32 (72.7)
Prior neovascular AMD treatment, n (%)			
Naive	30 (33.7)	15 (33.3)	15 (33.3)
Pre-treated[b]	59 (66.3)	30 (66.7)	29 (65.9)
Photodynamic therapy	0	0	0
Anti-VEGF	57	30	27
Number of anti-VEGF injections before SMH[c], mean±SD	13.3±10.6	14.5±10.7	11.8±10.5
Time since last AMD injection[d]			
< 1 year, n (%)	42 (73.7)	20 (66.7)	22 (81.5)
≥ 1 year, n (%)	15 (26.3)	10 (33.3)	5 (18.5)
Symptoms duration until SMH diagnosis, days[e]			
Mean±SD	4.8±4.4	4.3±4.1	5.2±4.7
Median (IQR)	3.5 (2.0-6.0)	3.0 (2.0-5.0)	4.0 (2.0-7.0)
Symptoms duration until SMH treatment,[f] days			
Mean±SD	7.5±4.4	7.4±4.7	7.6±5.1
Median (IQR)	7.0 (4.0-11.0)	6.5 (4.0-10.0)	7.0 (3.0-11.0)
VFQ-25 score, mean±SD[g]	59.1±21.6	53.9±20.0	64.6±22.1

Abbreviations: AMD=age-related macular degeneration, IQR=interquartile range, SD=standard deviation, IQR= interquartile range, SMH=submacular hemorrhage, VEGF=vascular endothelial growth factor

[a] missing data: n=6 in the surgery group and n=12 in the pneumatic displacement group

[b] missing data: n=2 in the pneumatic displacement group

[c] missing data: n=5 in the surgery group and n=5 in the pneumatic displacement group

[d] missing data: n=1 in the surgery group

[e] missing data: n=1 in the pneumatic displacement group

[f] missing data: n=1 in the surgery group and n=1 in the pneumatic displacement group

[g] missing data: n=6 in the surgery group and n=7 in the pneumatic displacement group

Table 3. Ocular clinical and imaging characteristics of the studied eyes, at enrolment visit

Characteristic	Overall n=89	Surgery group n=45	Pneumatic displacement group n=44
Visual acuity at time of SMH,			
ETDRS letters			
mean±SD	22.0±22.5	21.9±23.1	22.11±22.2
≥70 letters (20/40 or better), n (%)	2 (2.2)	1 (2.2)	1 (2.3)
≥35 letters (20/200 or better), n (%)	25 (28.1)	13 (28.9)	12 (27.3)
<35 letters (20/200 or worse), n (%)	62 (69.7)	31 (68.9)	31 (70.4)
SMH characteristics			
SMH thickness,[a] μm			
Mean±SD	1033.5±479.6	1098.0±585.2	965.9±329.6
Median (IQR)	1004.0 (767.5-1181.5)	1038.0 (842.0-1178.0)	939.0 (700.0-1185.0)
SMH largest diameter,[b] n (%)			
<2 DD	-	-	-
[2-5] DD	52 (64.2)	23 (56.1)	29 (72.5)
> 5 DD	29 (35.8)	18 (43.9)	11 (27.5)
Sub-RPE involvement,[c] n (%)			
Uninterpretable	3 (3.9)	2 (5.1)	1 (2.6)
Yes	64 (83.1)	33 (84.6)	31 (81.6)
No	10 (13.0)	4 (10.3)	6 (15.8)

Abbreviations: DD = disc diameter, ETDRS= Early Treatment of Diabetic Retinopathy Study, IQR=interquartile range, OCT=optical coherence tomography, RPE=retinal pigment epithelium, SD=standard deviation, SMH=submacular hemorrhage, VEGF=vascular endothelial growth factor, VFQ-25=Visual Function Questionnaire

[a] missing data: n=2 in the surgery group and n=3 in the pneumatic displacement group

[b] missing data: n=4 in the surgery group and n=4 in the pneumatic displacement group

[c] missing data: n=6 in the surgery group and n=6 in the pneumatic displacement group

Table 4. Visual, quality-of-life, and anti-VEGF treatment outcomes

	Surgery group	Pneumatic displacement group	Adjusted difference Surgery vs Pneumatic displacement β [95% CI] [d]	P value
Visual acuity, ETDRS letters				
Month 3 [a],	n=40	n=38		
Mean±SD	38.8±24.1	40.0±23.0		
Change from baseline	n=40	N=38		
Mean [95% CI]	16.8 [8.7; 24.9]	16.4 [7.1; 25.7]	1.9 [-11.0; 14.9] [b]	0.767 [b]
Median (IQR)	16.5 (0.5; 38.5)	15.0 (1.0; 34.0)		
Month 6 [a],	n=34	n=37		
Mean±SD	39.3±24.7	39.6±24.0		
Change from baseline				
Mean [95% CI]	17.2 [9.1; 25.4]	15.4 [5.7; 25.1]	3.3 [-10.5; 17.0] [b]	0.776 [b]
Median (IQR)	14.5 (1.0; 32.0)	10.0 (0; 33.0)		
Quality-of-life, VFQ-25 composite score				
Month 3 [a],	n=37	n=34		
Mean±SD	54.3±21.4	63.6±23.6	-0.5 [-8.3;7.2] [c]	0.888 [c]
Change from baseline	n=37	n=30		
Mean [95% CI]	-0.1 [-5.7; 5.4]	-3.3 [-9.1; 2.6]		
Median (IQR)	0.9 (-6.8; 9.1)	-4.2 (-10.0; 1.73)		
Month 6 [a],	n=34	n=31		
Mean±SD	57.5±22.1	60.4±24.0	5.7 [-2.2;13.6] [c]	0.152 [c]
Change from baseline	n=32	n=28		
Mean [95% CI]	3.9 [-0.5;8.2]	-5.0 [-11.9; 1.9]		
Median (IQR)	3.5 (-1.0; 11.2)	-3.7 (-12.3; 0.7)		
Anti-VEGF injections				
From Month 3 to 6 [a]	n=45	n=44		
At least one injection, n (%)	33 (73.3)	37 (84.1)		
Number of injections				
Mean±SD	3.2±1.0	2.8±1.2	0.1 [-0.1;0.4] [b]	0.334 [b]
Median (IQR)	4.0 (3.0; 4.0)	3.0 (2.0; 4.0)		

Abbreviations: CI=confidence interval, ETDRS=Early Treatment of Diabetic Retinopathy Study, IQR=interquartile range, SD=standard deviation, VEGF=vascular epithelial growth factor, VFQ-25=Visual Function Questionnaire.

[a] n represents the number of patients with observed data at a specific timepoint for each outcome. Means, medians, and percentages were calculated using observed data.

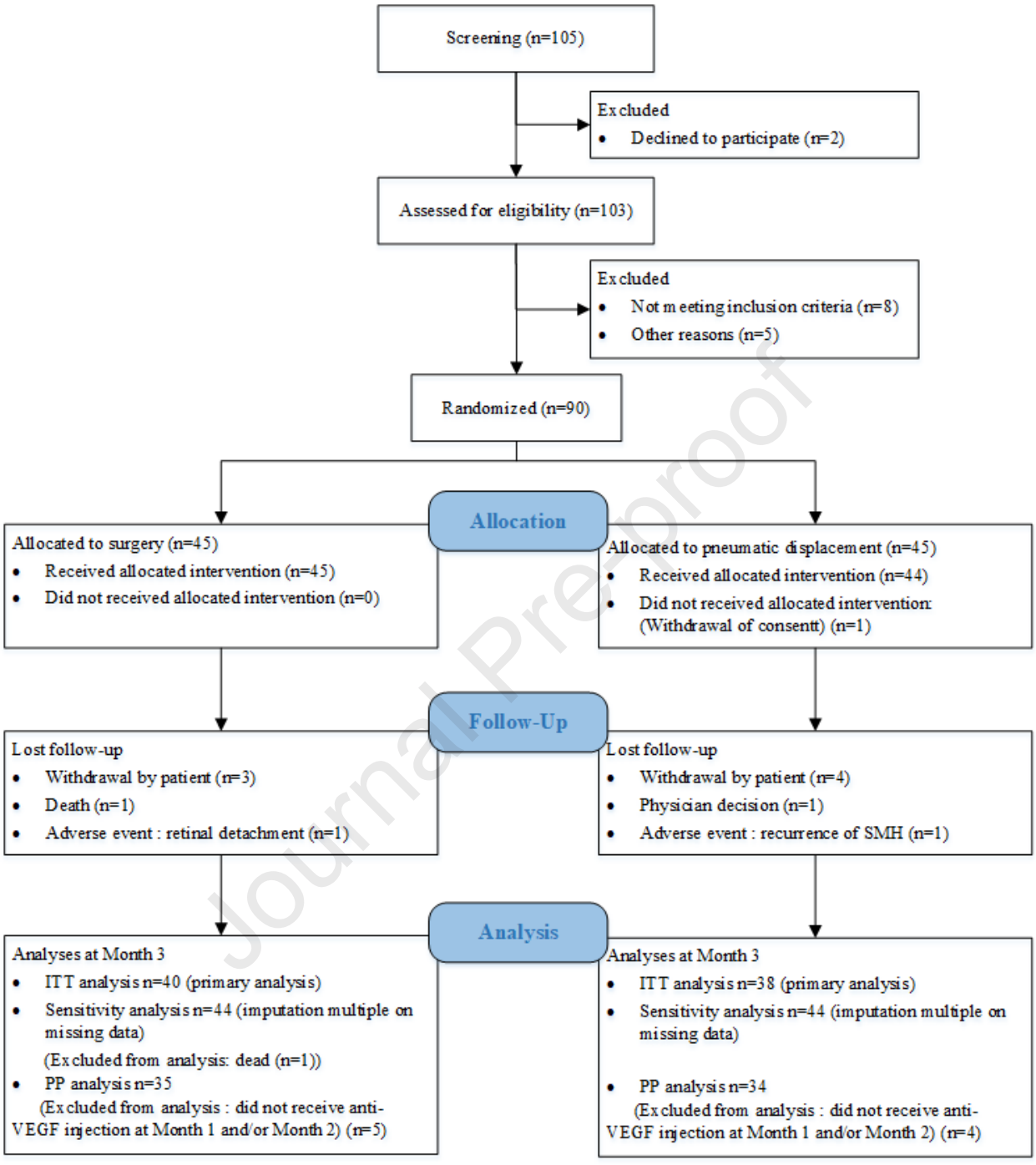
[b] Treatment group adjusted differences β, 95% CI, and P values were obtained using multiple linear regression model adjusted for randomization stratification factors (neovascular age-related macular degeneration pretreated status and center) and were based on observed data.

[c] Treatment group adjusted differences β, 95% CI, and P values were obtained using multiple linear regression model adjusted for randomization stratification factors and baseline VFQ-25 composite score and were based on observed data.

[d] A negative difference means that the outcome in the pneumatic displacement group was higher than the surgery group, a positive difference means the opposite.

Table 10. Ocular Adverse events related to the treatment procedure over the study period

	Surgery group n=45	**Pneumatic displacement group n=44**
Patients with ≥1 ocular adverse events, n (%)	12 (26.7)	12 (27.3)
Number of ocular adverse events, n		
Choroidal hemorrhage	1	0
Endophthalmitis	0	0
Retinal detachment	4	0
Vitreous hemorrhage	5	5
Hyphaema	1	0
Increased intraocular pressure	2	2
Recurrence of SMH	2	6
Macular hole	1	0
Cataract	2	2



ITT= Intention-To-Treat, PP=Per Protocol, SMH=submacular hemorrhage, VEGF=vascular endothelial growth factoR

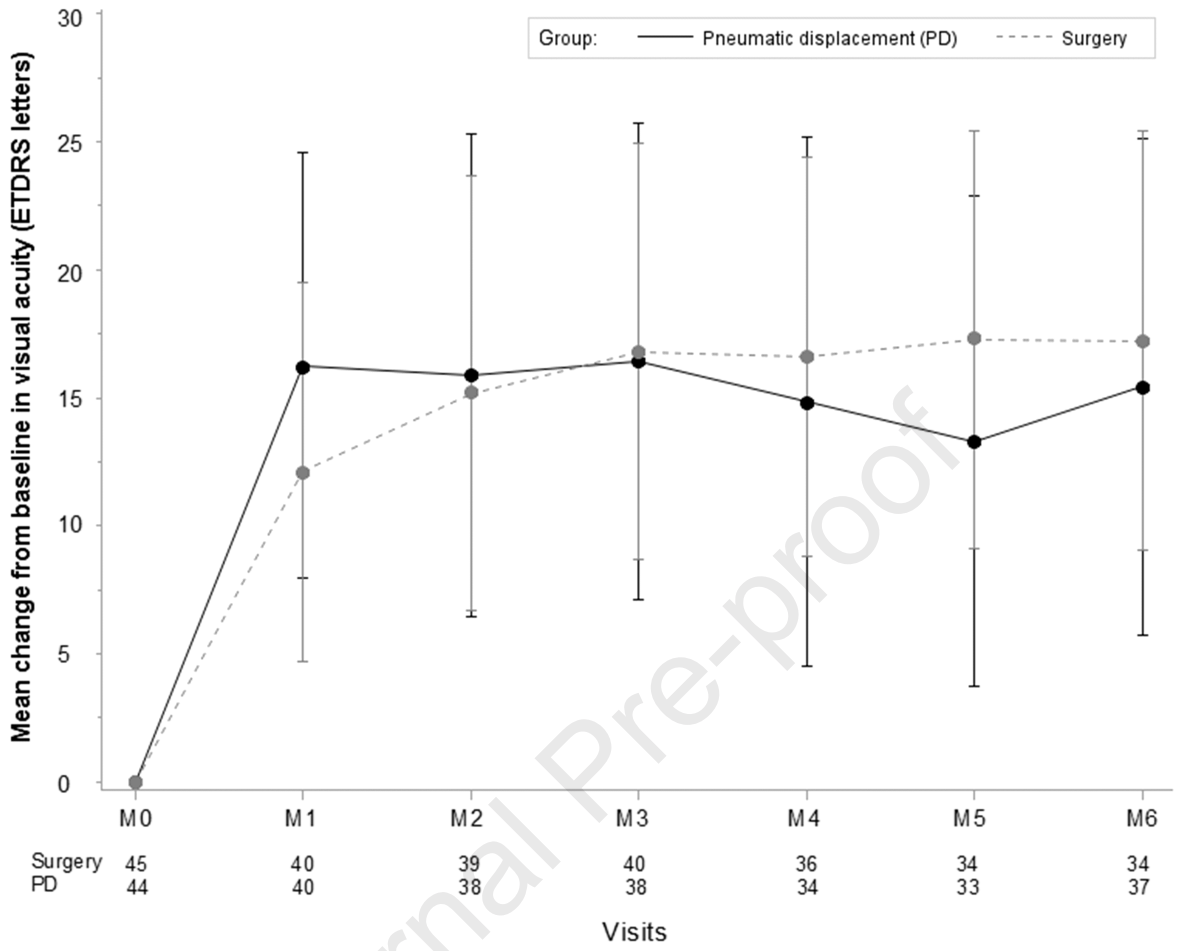


Figure S3. Mean change in visual acuity from baseline over the study period (per protocol analysis). The black spot represents the mean, and the upper and lower whisker extends to the superior and inferior value of the 95% confidence interval.

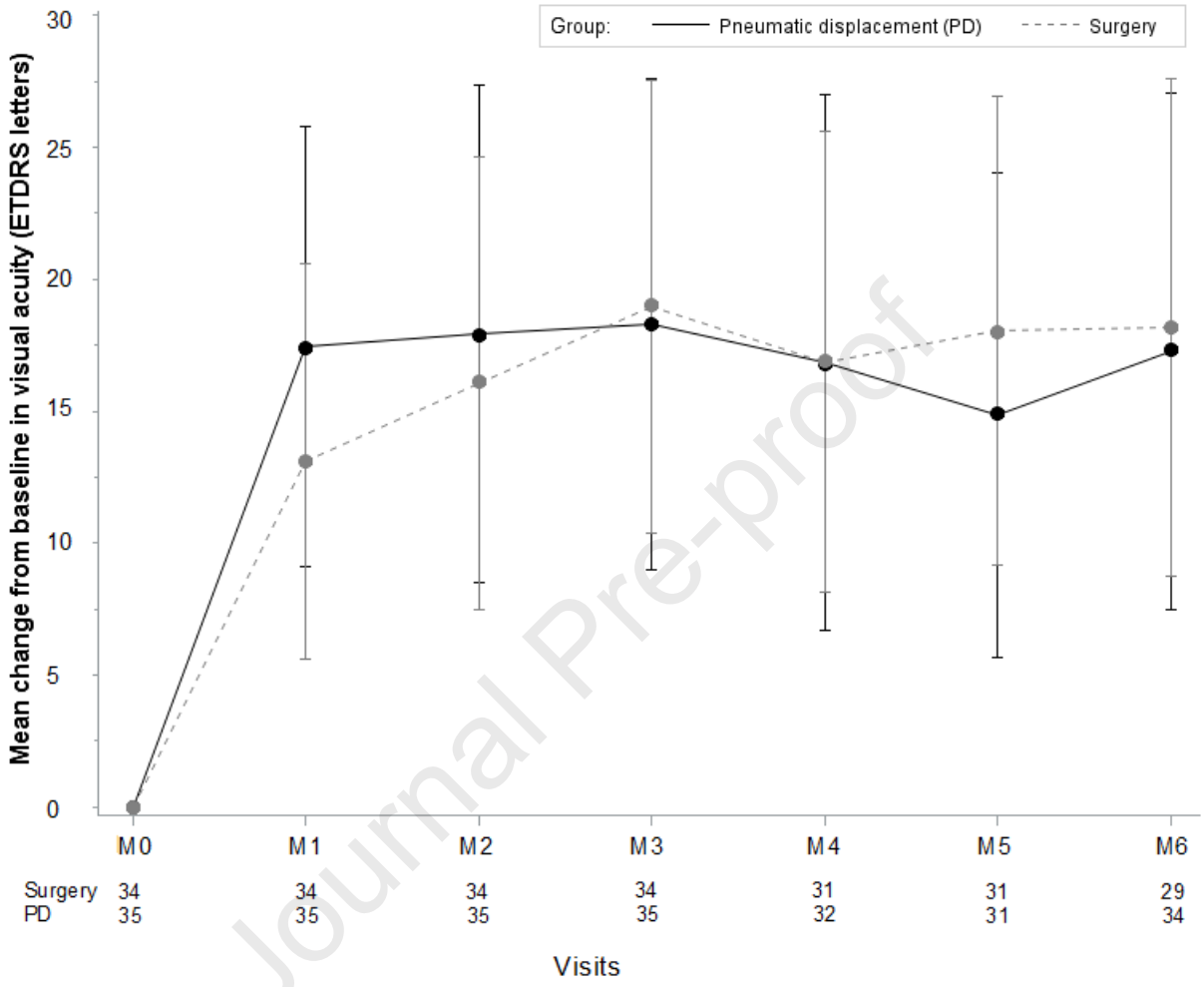


Figure S4. Percentage of patients with visual acuity gain ≥10 ETDRS letters over the study period.

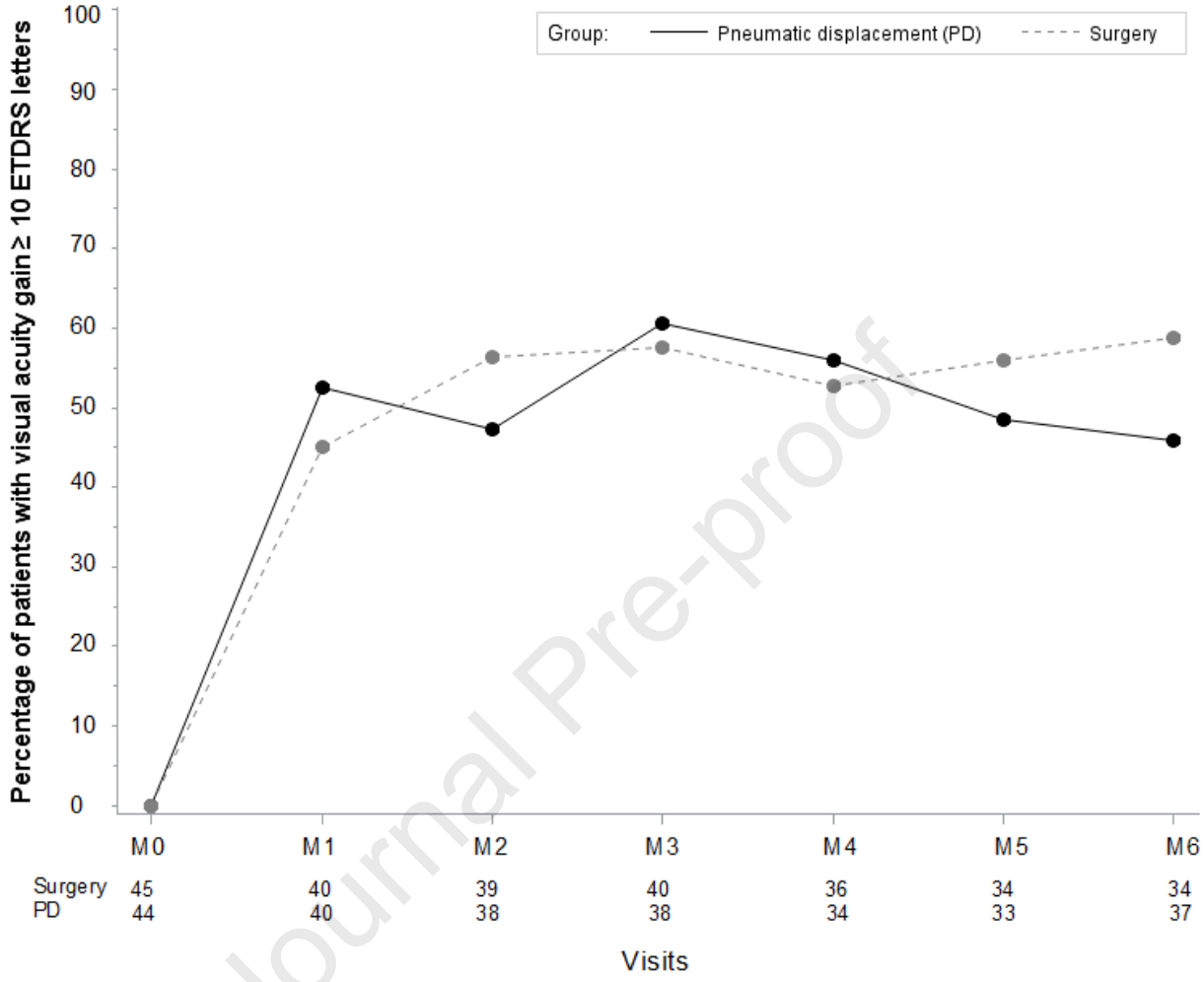


Figure S5. Percentage of patients with visual acuity gain ≥15 ETDRS letters over the study period.

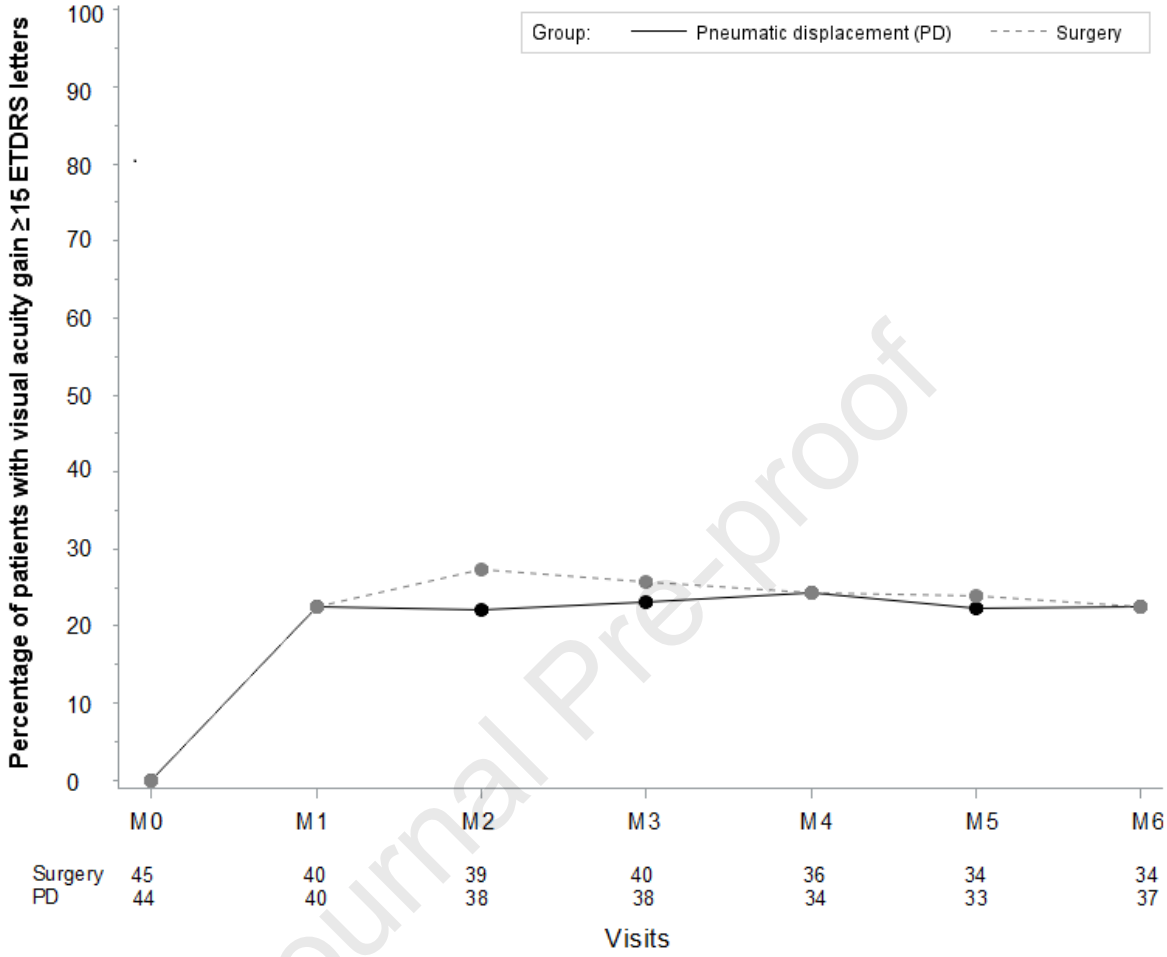


Figure S6. Percentage of patients with visual acuity worsening ≥10 ETDRS letters over the study period.

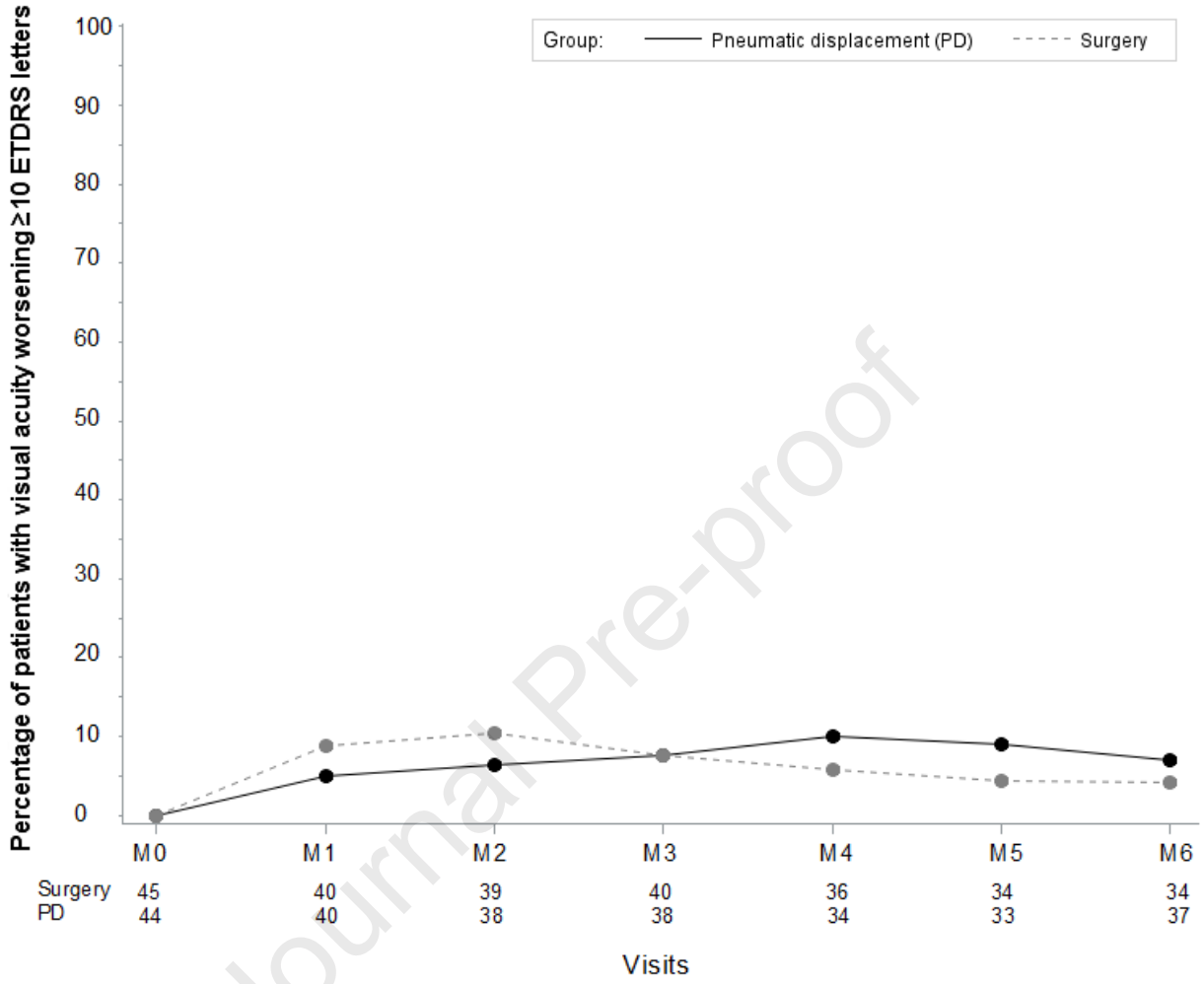


Figure S7. Percentage of patients with visual acuity worsening ≥15 ETDRS letters over the study period.

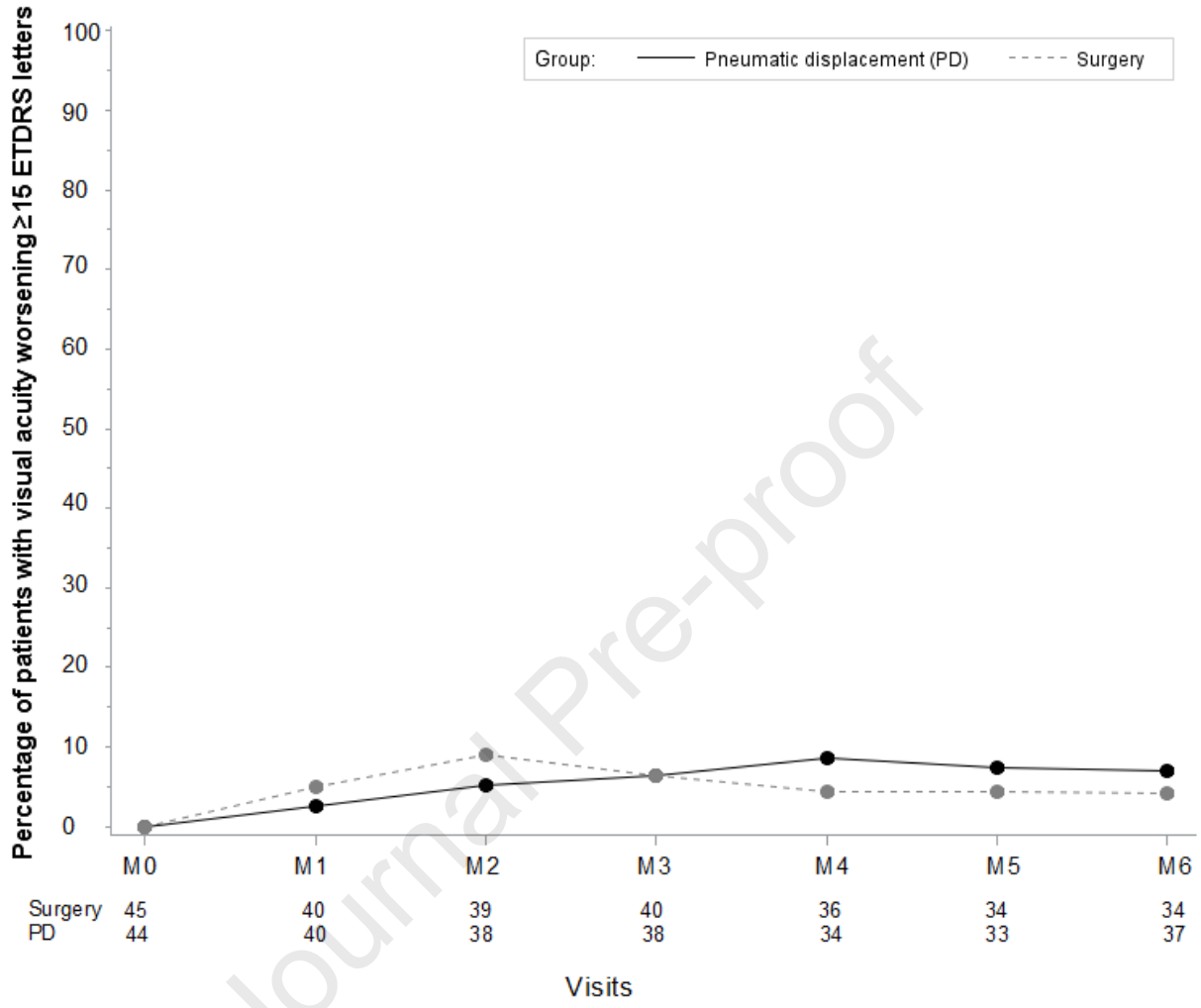


Table S2. Demographic and clinical characteristics of participants according to completion of Month 3 visit

	Completed Month 3 visit (n=78)	**Did not complete Month 3 visit (n=11)**	**P value**
Surgery group, n (%)	40 (51.3)	5 (45.5)	0.717[a]
Age, years, mean±SD	83.1±8.5	85.2±5.6	0.537[b]
Female, n (%)	54 (69.2)	5 (45.5)	0.172[c]
Study eye laterality (right), n (%)	43 (55.1)	5 (45.5)	0.547[a]
Comorbidities			
History of stroke, n (%)	3 (3.9)	2 (18.2)	0.113[c]
History of myocardial infarction, n (%)	8 (10.3)	0	0.589[c]
Systemic arterial hypertension, n (%)	48 (62.3)	10 (90.9)	0.089[c]
Type of antithrombotic therapy			
Anticoagulant, n (%)	22 (28.2)	4 (36.4)	0.724[c]
Antiplatelet agent, n (%)	23 (29.5)	3 (27.3)	1[c]
Visual acuity at baseline, ETDRS letters, mean±SD	22.8±22.3	16.3±24.1	0.379[b]

Abbreviations: ETDRS= Early Treatment of Diabetic Retinopathy Study, SD=standard deviation.

[a] Chi2 test

[b] Wilcoxon test

[c] Fisher exact test

Table S5. Visual outcomes at Month 3 (per protocol analysis**)**

	Surgery group n=34	**Pneumatic displacement group n=35**	**Adjusted difference Surgery vs Pneumatic displacement β [95% CI][a]**	**P value[a]**
Visual acuity,[b] ETDRS letters				
Mean±SD	40.8±23.1	42.3±22.5		
Median (IQR)	43.5 (26.0;55.0)	42.0 (26.0;60.0)		
Change from baseline,[b] ETDRS letters				
Mean [95% CI]	19.0 [10.4;27.6]	18.3 [9.0;27.6]	1.8 [-11.3;14.9]	0.787
Median (IQR)	20.0(5.0;39.0)	15.0 (1.0;36.0)		

Abbreviations: ETDRS= Early Treatment of Diabetic Retinopathy Study, IQR=interquartile range, SD=standard deviation.

[a] Treatment group adjusted differences β, 95% CI, and P values were obtained using a multiple linear regression model adjusted for randomization stratification factors (neovascular age-related macular degeneration pretreated status and center) and based on observed data. A negative difference means that the mean VA change in the pneumatic displacement group was higher than in the surgery group, a positive difference means the opposite.

[b] Mean±SD and medians (IQR) were calculated from observed data.

Table S6. Visual outcomes at Month 3 (sensitivity analyses)

			Multiple imputations for missing values		Adjustment for baseline SMH imbalanced characteristics	
	Surgery group n=40	**Pneumatic displacement group n=38**	**Adjusted difference Surgery vs. pneumatic displacement β [95% CI][a]**	**P value[a]**	**Adjusted difference Surgery vs. pneumatic displacement β [95% CI][b]**	**P value[b]**
Visual acuity,[c] ETDRS letters						
Mean±SD	38.8±24.1	40.0±23.0				
Median (IQR)	43.5 (17.5; 55.0)	39.0 (21.0; 55.0)				
Change from baseline,[c] ETDRS letters						
Mean [95% CI]	16.8 [8.7; 24.9]	16.4 [7.1; 25.7]	1.0 [-10.1; 12.0]	0.863	2.0 [-11.4; 13.5]	0.767
Median (IQR)	16.5 (0.5; 38.5)	15.0 (1.0; 34.0)				

Abbreviations: SMH= Submacular hemorrhage, ETDRS=Early Treatment of Diabetic Retinopathy Study, CI=confidence interval, IQR=interquartile range, SD=standard deviation.
[a]Treatment group adjusted differences β, 95% CI, and P values were obtained using a multiple linear regression model adjusted for randomization stratification factors (neovascular age-related macular degeneration pretreated status and center) with observed data and multiple imputations for missing data.
[b]Treatment group adjusted differences β, 95% CI, and P values were obtained using a multiple linear regression model adjusted for randomization stratification factors (neovascular age-related macular degeneration pretreated status and center) and baseline SMH imbalanced characteristics (SMH diameter and thickness).
A negative difference means that the mean VA change in the pneumatic displacement group was higher than in the surgery group, a positive difference means the opposite.
[c]Means and medians were calculated from observed 3-month data (n=4 and n=6 missing month 3 visual acuity in surgery and pneumatic displacement group, respectively).

Table S7. Visual acuity at Month 3 (subgroup analyses)

Subgroup	Surgery group		Pneumatic displacement group		P value for Interaction	Adjusted β Surgery vs. Pneumatic displacement [95%IC][a]	P value[a]
	n	Mean Visual Acuity Change from baseline ± SD	n	Mean Visual Acuity Change from baseline ± SD			
SMH Diameter [b c]					0.868		
2-5 DD	18	14.7±23.9	25	16.0±30.4		3.1 [-16.6; 22.8]	0.749
>5DD	18	21.8±24.3	9	18.3±29.9		4.2 [-20.2; 28.7]	0.718
SMH Thickness [b d]					0.546		
≤1000 µm	16	15.4±27.8	18	22.3±28.9		-0.2 [-22.4;22.1]	0.987
>1000 µm	22	17.0±24.6	17	9.6±29.5		3.3 [-17.0;23.7]	0.739

Abbreviations : CI=Confident Interval, SD=standard deviation, SMH=submacular hemorrhage

[a] Treatment group adjusted differences β [95% CI] and P values were obtained using multiple linear regression model adjusted for randomization stratification factors (neovascular age-related macular degeneration pretreated status and center) and based on observed data. A negative difference means that the mean VA change in the pneumatic displacement group was higher than in the surgery group, a positive difference means the opposite.

[b] Means ± SD were calculated from observed data.

[c] Data were missing for n=4 in the surgery group and n=4 in the pneumatic displacement group

[d] Data were missing for n=2 in the surgery group and n=3 in the pneumatic displacement group

Table S8. National Eye Institute Visual Functioning Questionnaire-25 over 3 months according to treatment groups.

	Baseline		Month 3		Change from baseline to month 3	
Domain score, mean±SD	**Surgery group** n=45	**Pneumatic displacement group** n=44	**Surgery group** n=40	**Pneumatic displacement group** n=38	**Surgery group** n=40	**Pneumatic displacement group** n=38
General Health[a]	44.2±19.4	49.3±16.1	42.6±19.4	52.2±14.7	-1.4±19.5	-1.7±18.5
General Vision[a]	48.7±17.6	47.6±18.5	50.3±16.8	57.1±18.5	2.7±16.4	8.0±20.7
Ocular Pain[a]	84.3±18.1	84.5±23.3	83.8±19.3	84.6±23.0	0±23.6	0.8±17.0
Near Activities[a]	52.2±28.9	59.5±31.2	46.4±30.4	57.0±29.7	-6.9±23.1	-6.3±20.6
Distance Activities[a]	51.9±27.2	63.0±32.4	52.6±29.2	65.0±32.8	-0.8±20.5	-2.5±30.3
Social Functioning[b]	73.0±28.3	75.3±32.6	73.0±26.1	79.4±27.5	-1.7±19.2	4.6±31.7
Mental Health[a]	36.9±24.3	54.2±28.8	38.2±26.8	53.7±30.2	0.3±22.3	-5.2±23.2
Role Difficulties[a]	38.1±32.4	56.4±33.2	43.2±34.6	52.6±34.9	3.0±26.8	-4.6±24.5
Dependency[a]	64.7±31.4	73.9±27.1	59.1±29.6	69.1±30.6	-4.7±19.5	-5.0±21.0
Driving[c]	17.1±26.0	52.7±40.0	19.7±32.9	47.1±41.4	-3.2±33.1	-11.0±29.9
Color Vision[d]	78.3±24.8	89.2±21.7	81.3±28.9	84.6±22.2	2.9±21.7	-3.3±18.3
Peripheral Vision[b]	58.6±28.6	74.3±27.9	68.2±26.1	74.3±28.5	8.3±27.4	0±26.3

[a] Data were missing for n=8 in the surgery group and for n=14 in the pneumatic displacement group
[b] Data were missing for n=9 in the surgery group and for n=17 in the pneumatic displacement group
[c] Data were missing for n=27 in the surgery group and for n=25 in the pneumatic displacement group
[d] Data were missing for n=10 in the surgery group and for n=14 in the pneumatic displacement group

Table S9. National Eye Institute Visual Functioning Questionnaire-25 over 6 months according to treatment groups.

	Baseline		Month 6		Change from baseline to Month 6	
Domain score, mean±SD	**Surgery group** N= 45	**Pneumatic displacement group** N=44	**Surgery group** N= 35	**Pneumatic displacement group** N=37	**Surgery group** N= 35	**Pneumatic displacement group** N=37
General Health[a]	44.2±19.4	49.3±16.1	44.1±19.5	50.0±22.4	1.6±17.9	-2.7±19.7
General Vision[a]	48.7±17.7	47.6±18.5	50.0±17.9	60.7±15.9	2.5±18.8	11.4±21.4*
Ocular Pain[a]	84.3±18.1	84.5±23.3	86.8±14.7	84.3±22.8	3.5±19.6	2.2±23.6
Near Activities[a]	52.2±28.9	59.5±31.2	51.5±30.3	55.4±28.2	-1.4±22.1	-5.1±24.7
Distance Activities[b]	51.9±27.2	63.0±32.4	57.8±30.8	61.1±33.5	5.2±21.3	-1.9±31.4
Social Functioning[c]	73.0±28.3	75.3±32.6	69.5±30.7	75.0±29.9	-5.2±17.0	3.7±29.8
Mental Health[a]	36.9±24.3	54.2±28.8	45.3±25.5	49.2±28.6	7.3±22.4	-8.5±24.4**
Role Difficulties[b]	38.1±32.4	56.4±33.2	47.4±33.9	50.4±33.7	10.2±24.7	-4.6±27.3*
Dependency[b]	64.7±31.4	73.9±27.1	64.4±32.4	58.9±35.8	1.3±21.1	-14.5±31.2*
Driving[d]	17.1±26.0	52.7±40.0	21.0±34.9	47.0±42.7	1.6±34.6	-13.0±42.9
Color Vision[c]	78.3±24.8	89.2±21.7	83.1±26.6	84.2±26.7	4.8±18.7	-3.7±22.7
Peripheral Vision[c]	58.6±28.6	74.3±27.9	64.7±29.6	74.2±27.5	8.1±26.9	2.8±28.9

[a] Data were missing for n=13 in the surgery group and for n=16 in the pneumatic displacement group
[b] Data were missing for n=13 in the surgery group and for n=17 in the pneumatic displacement group
[c] Data were missing for n=14 in the surgery group and for n=17 in the pneumatic displacement group
[d] Data were missing for n=29 in the surgery group and for n=28 in the pneumatic displacement group
* P value <0.05
** P value <0.01
P value obtained using Mann-Whitney test

Table S11. Ocular serious adverse events in the study eye, and relatedness to treatment

Eye disorders	Events	Severity	Treatment group	Relatedness to treatment
Vitreous haemorrhage	1	Severe	Pneumatic displacement group	Not related
Choroidal haematoma	1	Severe	Surgery group	Not related
Hyphaema	1	Severe	Surgery group	Not related

Table S12. Adverse events, excluding those in the study eye.

	Surgery group n=45	Pneumatic displacement group n=44
Patients with ≥1 adverse events, n (%)	24 (53.3)	18 (40.9)
System Organ Class, n		
Cardiac disorders		
Cardiac failure	3 [a]	1 [a]
Acute myocardial infarction	1	0
Ear and labyrinth disorders		
Vertigo	1	0
Eye disorders		
Anterior capsule opacification	1	0
Cataract	0	2
Conjunctival irritation	0	1
Corneal oedema	1	0
Dry eye	0	1
Eye pruritus	1	0
Eyelid hematoma	1	0
Recurrence of SMH	1	1
Vitreous hemorrhage	1	0
Infections and infestations		
Bronchitis	1	0
Erysipelas	1 [a]	0
Injury, poisoning and procedural complications		
Fall	1	0
Hip fracture	1	0
Femoral neck fracture	0	1 [a]
Fibula fracture	1	0
Ankle fracture	0	1
Femur fracture	1 [a]	0
Spinal fracture	1 [a]	0
Head injury	1 [a]	0
Gastrointestinal disorders		
Constipation	1 [a]	0
General disorders and administration site conditions		
Fatigue	1	0
Malaise	1 [a]	0
Musculoskeletal and connective tissue disorders		
Tendonitis	1	0
Neoplasms benign, malignant and unspecified		
Ovarian cancer	1 [a]	0
Nervous system disorder		
Cerebrovascular accident	1	0
Psychiatric disorders		
Procedural anxiety	1	0
Confusional state	1 [a]	0
Stress disorders	1	0
Reproductive system and breast disorders		

Genital Haemorrhage	0	1
Respiratory, thoracic and mediastinal disorders		
Lung disorder	1 [a]	0
Respiratory disorder	1 [a]	0
Vascular disorders		
Orthostatic hypotension	0	1
Arterial hypertension	2	1
Peripheral ischaemia	1 [a]	0

[a] declared as serious adverse events

Precis (35 words/35)

In a French randomized controlled trial (n=90, 6 months duration), surgical vitrectomy was not superior to pneumatic displacement in managing submacular hemorrhage secondary to age-related macular degeneration, with TPA and ranibizumab added to each arm.