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Hypotony Failure Criteria in Glaucoma Surgical Studies and Their Influence on Surgery Success

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	Main Outcome Measures Hazard ratio (HR) for failure risk. Results Of 2,503 studies found, 278 were eligible, with 99 (35.6%) studies lacking hypotony failure criteria. Numerical hypotony was predominant (157 studies [56.5%]). Few studies employed clinical hypotony (3 isolated [1.1%]; 19 combined with low IOP [6.8%]). Forty-nine different criteria were found, with IOP<6 mmHg, IOP<6 mmHg on ≥2 consecutive visits after 3 months, and IOP<5 mmHg being the most common (41 [14.7%], 38 [13.7%], and 13 [4.7%] studies, respectively). In both cohorts, numerical hypotony posed the highest risk of failure (HR between 1.51-1.21 for criteria A to D; p<0.001), followed by mixed hypotony (HR between 1.41-1.20 for criteria A to D; p<0.001), and clinical hypotony (HR between 1.12-1.04; p=0.07 for DS criteria D, p≤0.017 for other criteria). Failure risk varied greatly with various hypotony definitions, with HR ranging between 1.02-10.79 for trabeculectomy and 1.00-8.36 for DS. Discussion Hypotony failure criteria are highly heterogenous in the glaucoma literature, with few studies focusing on clinical manifestations. Numerical hypotony yields higher failure rates than clinical hypotony and can underestimate glaucoma surgery success rates. Standardizing failure criteria with an emphasis on clinically relevant hypotony manifestations is needed.
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December 26th, 2023

Russell N. Van Gelder, MD PhD
Chief Editor
Ophthalmology

Dear Editor,

Thank you for considering our manuscript OPHTHA-D-23-01936, “Hypotony Failure Criteria in Glaucoma Surgical Studies and Their Influence on Surgery Success" for publication in the Ophthalmology journal. The points raised by the EBM have all been considered and changes incorporated into the revised manuscript where appropriate. Attached is a point-by-point response to each of these comments. Any changes to the manuscript are italicized and in quotes in the response letter.

All the authors have approved the revised manuscript for submission to the Ophthalmology journal. As Corresponding Author, I had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, as well as the decision to submit it for publication.

Thank you for your consideration of our manuscripts and we look forward to your response.

Yours sincerely,

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Suggestion, Question, or Comment from the EBM/AE	Authors' Response	Change in the Manuscript
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PRECIS

Hypotony failure criteria are highly heterogenous in glaucoma surgical outcome studies, with few studies focusing on clinical manifestations. The choice of criteria significantly affects the measured (or calculated) success rates, highlighting the need for standardization.

- Manuscript–

Hypotony Failure Criteria in Glaucoma Surgical Studies and Their Influence on Surgery Success

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ABSTRACT

Purpose: Review hypotony failure criteria used in glaucoma surgical outcome studies and evaluate their impact on success rates.

Design: Systematic literature review and application of hypotony failure criteria to two retrospective cohorts.

Participants: 934 eyes and 1,765 eyes undergoing trabeculectomy and deep sclerectomy (DS) with a median follow-up of 41.4 and 45.4 months, respectively.

Methods: Literature-based hypotony failure criteria were applied to patient cohorts. IOP-related success was defined as: (A) IOP≤21 mmHg with ≥20% IOP reduction; (B) IOP≤18 mmHg with ≥20% reduction; (C) IOP≤15 mmHg with ≥25% reduction; (D) IOP≤12 mmHg with ≥30% reduction. Failure was defined as: IOP exceeding these criteria in two consecutive visits >3 months after surgery, loss of light perception, additional IOP-lowering surgery, or hypotony. Cox regression estimated failure risk for different hypotony criteria, using no hypotony as a reference. Analyses were conducted for each criterion and hypotony type (i.e., numerical [IOP threshold], clinical [clinical manifestations], mixed [combination of numerical and/or clinical criteria]).

Main Outcome Measures: Hazard ratio (HR) for failure risk.

Results: Of 2,503 studies found, 278 were eligible, with 99 (35.6%) studies lacking hypotony failure criteria. Numerical hypotony was predominant (157 studies [56.5%]). Few studies employed clinical hypotony (3 isolated [1.1%]; 19 combined with low IOP [6.8%]). Forty-nine different criteria were found, with IOP<6 mmHg, IOP<6 mmHg on ≥2 consecutive visits after 3 months, and IOP<5 mmHg being the most common (41 [14.7%], 38 [13.7%], and 13 [4.7%] studies, respectively). In both cohorts, numerical hypotony posed the highest risk of failure (HR between 1.51-1.21 for criteria A to D; p<0.001), followed by mixed hypotony (HR between 1.41-1.20 for criteria A to D; p<0.001), and clinical hypotony (HR between 1.12-1.04; p=0.07 for DS criteria D, p≤0.017 for other criteria). Failure risk varied greatly with various hypotony definitions, with HR ranging between 1.02-10.79 for trabeculectomy and 1.00-8.36 for DS.

Discussion: Hypotony failure criteria are highly heterogenous in the glaucoma literature, with few studies focusing on clinical manifestations. Numerical hypotony yields higher failure rates than

clinical hypotony and can underestimate glaucoma surgery success rates. Standardizing failure criteria with an emphasis on clinically relevant hypotony manifestations is needed.

Keywords: antimetabolites; choroidal effusion; glaucoma surgery; hypotony maculopathy; intraocular pressure; nonpenetrating glaucoma surgery; post-operative complications; randomized controlled study; retrospective study; trabeculectomy.

INTRODUCTION

Intraocular pressure (IOP) reduction is currently the only proven treatment to slow the progression of glaucoma, and it is achieved through medical, laser, and surgical treatments.[1] Glaucoma surgery has been traditionally reserved for eyes with uncontrolled disease despite medical and laser therapies. Previous studies have shown that glaucoma surgery effectively lowers IOP and reduces glaucomatous progression rates.[2, 3] Glaucoma surgery can provide a robust and sustained reduction in IOP, prevent further glaucoma deterioration, and preserve vision-related quality of life.

Postoperative hypotony can occur as a result of glaucoma surgery. The definition of hypotony varies in the literature and is usually categorized as numerical or clinical. Numerical hypotony is defined as an IOP below a certain threshold that is considered non-physiological and carries a risk of severe complications.[4] Clinical hypotony focuses more on the presence of complications caused by low IOP, regardless of the IOP reading. Some of these complications (e.g., hypotony maculopathy, choroidal hemorrhage) may be particularly serious and lead to irreversible loss of vision.[5, 6]

To standardize glaucoma surgery studies, the World Glaucoma Association (WGA) has issued guidelines for designing and reporting glaucoma surgical studies.[7] These guidelines recommend persistent numerical hypotony (i.e., IOP <6 mmHg for two consecutive examinations) as one of the failure criteria. Following WGA guidelines, persistent hypotony was set as a criterion for failure in many studies, including landmark surgical studies.[8-12] However, recent studies have questioned whether simple numerical hypotony truly reflects surgical outcomes.[13, 14] Most eyes with low IOP do not develop complications,[14, 15] and their outcomes are not significantly different from those without hypotony in terms of visual acuity, reoperation rates, and surgical failure.[13, 14] Additionally, patients with predisposing factors may experience sight-threatening hypotony complications even in the absence of numerical hypotony.[14, 15] Therefore, the widespread use of numerical hypotony as a failure criterion seems inappropriate, as it can misclassify successful operations as surgical failures and vice versa. Few studies[16-19] have adopted alternative definitions of hypotony failure based on the presence of hypotony complications alone or in combination with a low IOP cutoff.

The lack of consistency in defining failure criteria due to hypotony increases the heterogeneity of the literature, making it difficult to compare results from different studies. Abbas and colleagues[20] conducted a study evaluating how fourteen different hypotony failure definitions affected the proportion of patients labeled as having hypotony, and they found wide variations in hypotony prevalence depending on the criterion used. The impact of using different hypotony criteria for failure on success rates of glaucoma surgery is still unknown. The use of numerical criteria, such as the one proposed by the WGA guidelines, may disproportionately penalize techniques that can achieve a more substantial reduction in IOP (e.g., trabeculectomy) compared to less potent surgeries (e.g., plate-less bleb-forming devices, aqueous shunts).

In this study, we systematically review hypotony definitions used in the literature and assess the impact of different hypotony failure criteria on glaucoma surgery success rates in two large cohorts of patients undergoing trabeculectomy and deep sclerectomy (DS) with long-term follow-up.

METHODS

Publication Search and Assessment

We conducted a systematic literature review (PROSPERO CRD42022378096) in PubMed using the following search terms: Ahmed valve, Baerveldt, deep sclerectomy, express shunt, glaucoma drainage device, glaucoma operation, glaucoma surgery, glaucoma tube, glaucoma valve, Innfocus, Preserflo Microshunt, Trabeculectomy, Xen gel stent, Xen implant, Xen Stent. We limited the results to clinical studies, clinical trials (all types), comparative studies, multicenter studies, and observational studies. We included articles published in English on human patients from January 1, 2010 to November 21, 2022. This time frame encompassed studies published within a year after the introduction of the World Glaucoma Association (WGA) consensus document on reporting glaucoma surgical studies up to the design of our study.[7] We included studies that reported success rates of glaucoma surgical procedures performed alone or in conjunction with other ocular surgeries (e.g., cataract surgery). We included surgical techniques that provided subconjunctival filtration, either *ab externo* (e.g., trabeculectomy, glaucoma drainage devices, deep sclerectomy, Preserflo MicroShunt, Express shunt) or *ab interno* (e.g., Xen Gel). We excluded other surgeries targeting the trabecular meshwork and suprachoroidal space as these techniques have different indications, IOP-lowering efficacy, and rarely lead to hypotony. We did not include studies on glaucoma laser procedures or medications for the same reasons. If a study compared different surgical techniques, it was included as long as at least one of the study procedures met our inclusion criteria. We used the Rayyan web application[21] to screen titles and abstracts of potentially eligible studies. Prior to data screening, we removed studies with duplicated information or those not primarily written in English.

Two independent investigators (AR and GT) screened the titles and abstracts to select studies for full-text review. The reviewers were masked to each other's decisions until the study selection was completed. Disagreement was resolved with open adjudication between the two investigators. If no agreement could be reached, a third investigator was involved to make the final decision. For those studies that passed the screening process, we obtained the full text through PubMed, journal website or other sources. If articles could not be found, we contacted the corresponding authors to request a copy. If there was no response from the corresponding author within four weeks, the article was excluded from the full-text review.

The same two investigators independently extracted relevant information, including the specific definition of hypotony used as a failure criterion and the type of hypotony. The type of hypotony was classified as numerical (based on intraocular pressure thresholds only), clinical (based on clinical manifestations of hypotony only), or mixed (a combination of numerical and/or clinical criteria).

The reviewers were masked to each other's decisions until the data extraction was completed. Disagreements were resolved through open adjudication between the two investigators. If an agreement could not be reached, a third investigator was involved to make the final decision.

Patients' cohorts

Two large retrospective clinical datasets of patients undergoing either trabeculectomy or nonpenetrating deep sclerectomy were included.

The trabeculectomy dataset included patients who underwent trabeculectomy between 1999 and 2022 at the Glaucoma Division of the Stein Eye Institute, University of California, Los Angeles. Surgeries were performed or supervised by one of the five attendings using a previously reported technique.[22-24] The use of this dataset was approved by the institution review board (IRB) at the University of California, Los Angeles and adhered with the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. The IRB waived the requirement for written informed consent.

The deep sclerectomy dataset consisted of consecutive patients who underwent deep sclerectomy in two UK glaucoma services: Calderdale and Huddersfield NHS Foundation Trust (between 2001 and 2014) and Gloucestershire Hospitals NHS Foundation

Trust (between 2014 and 2020). The patients were under the care of a single glaucoma and anterior segment surgeon (NA). All data were fully anonymized prior to analysis. The surgical procedures were either performed or supervised by an experienced glaucoma surgeon (NA) and followed a standardized technique described in previous publications.[14, 25-27] This study did not directly involve human subjects, identifiable human material, or identifiable data. According to UK legislation, the use of a retrospective dataset for anonymized database analyses is considered an audit or service evaluation and does not require IRB approval. The study adhered to the principles outlined in the Declaration of Helsinki, the United Kingdom Data Protection Act, and the National Institute for Health Research guidance. The retrospective anonymized data extraction was approved by the Calderdale and Huddersfield NHS Foundation Trust and the Gloucestershire Hospitals NHS Caldicott Guardians, who are responsible for information governance.

From the two datasets, we used the following preoperative variables for the analysis: eye and patient identification numbers, age, ethnicity, laterality, central corneal thickness (CCT), Snellen best-corrected visual acuity (BCVA), IOP measured with Goldmann applanation tonometry, number of topical antiglaucoma agents, use of systemic acetazolamide, visual field mean deviation (MD), glaucoma subtype, lens status, previous laser trabeculoplasty, previous glaucoma, lens, corneal, and retinal surgery and their type. Intraoperative variables included whether the trabeculectomy or DS was performed stand-alone or combined with other ocular procedures. Postoperative variables were collected for any available visit and included: IOP, BCVA, postoperative complications occurrence, their type and their grade (where available), revision surgery and its reasons (e.g., hypotony, dystesthesia), other subsequent glaucoma surgery or ciliodestructive procedure. If an eye underwent further glaucoma surgery, we censored its follow-up at the time of the listing visit. We included both eyes of the same patient if eligible. If the same eye underwent two or more glaucoma surgery in the study period, we included the first available surgery. We excluded eyes in which preoperative IOP and BCVA were not available as this prevented the calculation of success rates. No other inclusion/exclusion criteria were applied.

Criteria for success

Four different upper IOP cutoff were chosen as criteria for success: (A) IOP≤21 mmHg with ≥20% IOP reduction from preoperative values; (B) IOP≤18 mmHg with ≥20% IOP reduction; (C) IOP≤15 mmHg with ≥25% IOP reduction; (D) IOP≤12 mmHg with ≥30% IOP reduction. Failure was defined as follows: IOP above the specified criteria in two consecutive visits three months after surgery, loss of light perception, additional IOP-lowering glaucoma surgery or ciliodestructive procedures, and hypotony. We applied each of the different hypotony criteria identified in the systematic review to the patient cohort sequentially. For each dataset, we calculated multiple success rates corresponding to the different hypotony criteria identified in the literature that were replicable. By keeping the first three failure criteria fixed and varying only the definition of hypotony, we were able to evaluate the impact of different hypotony failure criteria. Hypotony complications were defined as the presence of one or more of the following: reduced AC depth with any degree of iris-corneal touch, hypotony maculopathy, choroidal effusion, choroidal hemorrhage, hypotony keratopathy, and decompression retinopathy.

Statistical Analysis

Statistical analysis was performed with the open-source software R (R Foundation for Statistical Computing, Vienna, Austria). All tests were 2-tailed, and p-values <0.05 were considered statistically significant. We converted Snellen visual acuity values to the logarithm of the minimum angle of resolution (logMAR) scale. Continuous variables were reported as mean (± standard deviation [SD]) or median (interquartile range [IQR]), and categorical variables as frequencies or proportions.

Differences in demographic and preoperative variables between the two cohorts were tested. Differences in patient-related categorical variables (e.g., ethnicity) were tested with the chi square test. Differences in eye-related variables (e.g., BCVA, IOP) were tested with a mixed model, where the patient identification number was included as a random effect to account for the inclusion of the two eyes from the same patients. We used linear mixed models (package *lme4*)[28] and generalized mixed models with adaptive Gaussian quadrature (package *GLMMadaptive*)[29] for continuous and categorical variables, respectively. Multinomial categorical variables, such as type of glaucoma, baseline lens status, and surgical procedure, were binarized using the most prevalent category as the reference level.

We used Kaplan-Meir survival curves to calculate the overall cumulative incidence of hypotony and success based on the various IOP criteria. We clustered data for the patient identification number to account for the inclusion of two eyes of the same patient, and a robust variance estimate based on the infinitesimal jackknife estimate was used to calculate unbiased standard errors.[30] We conducted analyses separately for each criterion and type of hypotony (i.e., numerical, clinical, mixed). We generated Venn diagrams to visualize the relationships between clinical hypotony and hypotony failure criteria most commonly reported in the literature. We calculated the sensitivity and specificity of each numerical criterion to diagnose the presence of hypotony complications. We ran clustered Cox regression analyses with robust variance estimation (to account for within-data correlations) to test differences between groups and estimate the risk of failure according to the various criteria when having no hypotony failure criterion as a reference. We employed the Tukey method for pairwise comparison.

RESULTS

Systematic Review

We initially identified 2,503 studies through the database search (Figure 1). After excluding 201 studies with duplicate information and 24 studies not in English, we screened 2,278 unique abstracts. Among these, 291 abstracts met the eligibility criteria and underwent full-text review. From the eligible studies, thirteen studies were further excluded due to reasons such as duplicated information (n=6), unavailability of full text (n=3), absence of reported success rates (n=2), cross-sectional design (n=1), and the use of a suprachoroidal device (n=1). Hypotony failure definitions were extracted from the remaining 278 articles.

Out of the included studies, 99 (35.6%) did not use any hypotony failure criteria. Numerical hypotony was the most commonly adopted failure criterion, present in 157 studies (56.5%). Only a small number of studies incorporated clinical complications of hypotony as failure criteria, either in isolation (3 studies [1.1%]) or in combination with a low IOP cutoff (19 studies [6.8%]). When the prevalence of hypotony failure criteria was stratified as a function of the year of publication (Figure S2), the proportion of studies with no hypotony failing criteria progressively decreased from 61.5% in 2010 to 8.3% in 2022. Conversely, the proportion of studies using numerical hypotony progressively increased from 30.8% in 2010 to 75% in 2022. The use of mixed hypotony and clinical hypotony was inconsistent and did not follow any trend.

Figure S3 illustrates that a total of forty-nine specific hypotony failure criteria were identified, with IOP<6 mmHg, IOP<6 mmHg on ≥2 consecutive visits after 3 months from surgery, and IOP<5 mmHg being the most frequently used failure criteria in 41 (14.7%), 38 (13.7%), and 13 (4.7%) studies, respectively. One of the 49 hypotony failure criteria (i.e., sustained IOP<5 mmHg)[31, 32] could not be applied to our patient cohorts as the authors did not provide enough details to make them replicable, particularly with regards to the period of time required to define hypotony as "sustained".

Patient Cohorts

A total of 934 eyes of 766 patients and 1,765 eyes of 1,385 patients were included in the trabeculectomy and deep sclerectomy cohorts, respectively. The median (IQR) follow-up was 41.4 (19.3 – 74.8) months and 45.4 (20.9 – 79.8) months in the trabeculectomy and DS cohort, respectively. Table 1 illustrates the demographic and clinical characteristics of the included patients.

Hypotony incidence

Figure 4 illustrates the cumulative incidence of hypotony in the two patient cohorts. In both cohorts, numerical hypotony (i.e., intraocular pressure thresholds only) had the highest cumulative incidence, followed by mixed hypotony (i.e., a combination of numerical and/or clinical criteria), and clinical hypotony (i.e., clinical manifestations of hypotony only). Differences in hypotony incidence, as estimated with different hypotony types, were statistically significant for all pairwise comparisons ($p<0.001$).

With regards to the specific hypotony criteria (Table S2), the median (IQR) 5-year estimated incidence (95% CI) of hypotony was 18.9% (11.3%-30.2%) and 8.0% (5.1%-16.8%) for the trabeculectomy and DS, respectively. Among the three most commonly used criteria in the literature (Table 3), IOP<6 mmHg led to the highest estimated 5-year incidence of hypotony, followed by IOP<5 mmHg, and, considerably lower, IOP<6 mmHg on ≥2 consecutive visits after 3 months from surgery. Among clinical hypotony criteria, the use of hypotony complications led to the highest estimated 5-year incidence of hypotony, followed by hypotony maculopathy, and surgical reoperation for hypotony. As shown in Figure 5, a sizable proportion of patients categorized as “failed” due to hypotony with the two most used criteria (i.e., IOP<6 mmHg, IOP<6 mmHg on ≥2 consecutive visits after 3 months) did not experience any clinical complication. Conversely, only 4 (0.4%) and 5 (0.3%) patients in the trabeculectomy and DS cohorts, respectively, developed complications despite not meeting these numerical hypotony thresholds. Table 4 presents the sensitivity and specificity values of each numerical hypotony criterion for identifying clinical complications. No specific criterion demonstrated strong diagnostic properties. In general, criteria that did not impose any time cutoff from the original surgery and did not require confirmation of IOP readings in subsequent visits tended to have higher sensitivity but lower specificity. This suggests that they were more likely to detect hypotony complications but also had a higher rate of false positives. Conversely, criteria that included a time cutoff from surgery and required low IOP in multiple visits or at the last visit tended to have higher specificity but lower sensitivity. These criteria were more precise in confirming hypotony complications but might miss early or transient hypotony complications.

Surgical success rates by hypotony type

Figure S6 and Table S5 illustrate the success rates of the two surgical procedures as a function of the type of hypotony. The 5-year success rates for trabeculectomy and DS were highest with no hypotony failure criteria (criteria A-D: trabeculectomy 40.9-23.2%; DS: 62.4-15.0%), followed by clinical hypotony (criteria A-D: trabeculectomy 37.9-21.5%; DS: 59.7-13.8%), mixed hypotony (criteria A-D: trabeculectomy 31.7-16.7%; DS: 54.2-11.7%), and numerical hypotony (criteria A-D: trabeculectomy 28.3-13.7%; DS: 52.6-11.0%).

Figure S7 and Table S6 illustrate the results of the Cox regression analysis based on the hypotony type compared to having no hypotony failure criteria. In both cohorts, numerical hypotony posed the highest risk of labeling a patient as a failure (trabeculectomy HR between 1.51-1.41 for criteria A to D; $p<0.001$; DS HR between 1.46-1.21 for criteria A to D; $p<0.001$), followed by mixed hypotony (trabeculectomy HR between 1.40-1.31 for criteria A to D; $p<0.001$; DS HR between 1.41-1.20 for criteria A to D; $p<0.001$), and clinical hypotony (trabeculectomy HR between 1.12-1.09 for criteria A to D; $p<0.001$; DS HR between 1.10-1.04 for criteria A to D; $p<0.001$). The impact of different hypotony criteria was considerably reduced with more stringent IOP upper cutoffs in the DS cohort, while it only slightly decreased in the trabeculectomy cohort.

Surgical success rates by specific hypotony criteria

As shown in Figure S8 and Tables S7 and S8, estimated success rates varied greatly as a function of the specific hypotony criterion chosen. Among the three most commonly used criteria in the literature (Table 9), IOP<6 mmHg on ≥2 consecutive visits after 3 months from surgery led to the highest 5-year success rates for all criteria, followed by IOP<5 mmHg, and IOP<6 mmHg. Regarding clinical hypotony (Table 9), the 5-year success rates were the highest using the presence of hypotony maculopathy, followed by surgical revision for hypotony, and hypotony complications.

Figure S9 and Tables S10 and S11 detail the risk of failure using the various individual criteria having no hypotony failure criteria as a reference in the two cohorts of patients. Among the three most commonly used criteria, IOP<6 mmHg led to the highest risk of failure, followed by IOP<5 mmHg, and IOP<6 mmHg on ≥2 consecutive visits after 3 months from surgery. When looking at clinical hypotony criteria, hypotony complications were significantly ($p<0.001$) associated with an increased risk of failure. Using hypotony maculopathy or revision for hypotony complications marginally increased the risk of failure compared to having no hypotony failure criteria.

DISCUSSION

In this study, we conducted a systematic literature review to identify the definitions of hypotony used as failure criteria in glaucoma surgical outcome studies. We then applied the identified criteria to two large cohorts of patients undergoing trabeculectomy and DS surgery. We found that hypotony failure criteria were highly heterogeneous in the current literature, with 49 distinct criteria identified. Additionally, most studies either lacked hypotony failure criteria altogether or relied on numerical cutoffs, and only a few studies focused on clinically relevant hypotony manifestations. When we applied the various hypotony criteria to our two patient cohorts, we observed a substantial impact on the incidence of hypotony and the success rates. The choice of hypotony criterion significantly influenced the results, with the use of numerical hypotony only leading to a likely underestimation of true surgical success rates. This result is particularly meaningful given the long follow-up time, which would have allowed us to detect clinically significant consequences of hypotony.

The goal of any glaucoma treatment is to slow glaucoma progression, preventing visual disability and loss of vision-related quality of life. As such, the use of visual field and its progression rates as a primary outcome for surgical success has been advocated.[33, 34] However, visual field progression has been infrequently used as a primary outcome in glaucoma surgical studies. Despite being an imperfect surrogate measure for disease progression, IOP control has been routinely used to gauge the success of surgical techniques. Historical studies, however, were highly heterogeneous in defining tonometric success, and the specific set of criteria used to define IOP control influenced estimated success rates.[35] Historical literature gave little emphasis to hypotony, with most studies having no hypotony criteria.[35] In 2009, the World Glaucoma Association (WGA) released a consensus document on designing and reporting glaucoma surgical studies to provide some standardization.[7] The WGA consensus introduced a numerical hypotony criterion for failure, defining failure as an IOP<6 mmHg (preferably on two consecutive visits). The tube-versus-trabeculectomy (TVT) study[36] chose to adopt variations of the WGA hypotony criteria, introducing a window of three months from the original surgery to overcome the impact of early hypotony. Early hypotony may be relatively frequent after glaucoma surgery, and the IOP behavior in the early postoperative visits may not reflect long-term IOP control. As a consequence of the WGA guidelines and study design of milestone studies, the number of studies incorporating some form of hypotony failure criteria progressively increased over time, with fewer than one in ten studies lacking such criteria in 2022. Our work also revealed that the heterogeneity in hypotony failure criteria remains very high in the current literature, with approximately one diverse criterion in every five published studies. One-third of the studies used an IOP threshold similar to those recommended by the WGA (IOP<6 mmHg or IOP≤6 mmHg) or the TVT study. This finding, in conjunction with the progressive incorporation of hypotony failure criteria, confirms that consensus documents and milestone studies have the potential to impact research methods and the clinical care of glaucoma.

Although the use of a numerical cutoff is simple and convenient, recent studies[13, 14] have shown that numerical hypotony is a poor surrogate for the presence of clinically significant hypotony. In our study (Figure 5), most patients with numerical hypotony did not develop any complications. Conversely, approximately 0.3-0.4% of patients with no numerical hypotony experienced hypotony complications. This finding aligns with previous studies indicating higher risk of complication, such as hypotony maculopathy, choroidal hemorrhage, or choroidal effusion, in certain patient categories. These include young patients with more elastic sclera, myopes with thinner sclera, and vitrectomized patients lacking vitreous body support for the sclera.[14, 15, 37] In these patients, hypotony complications may occur at IOP values considered 'normal' by a numerical definition of hypotony. Therefore, numerical hypotony is neither sufficient nor necessary to develop hypotony complications. We found that the use of clinical hypotony as a criterion for failure is very uncommon, with no evident increasing trend in recent years. This suggests that recent articles pointing out the fallacy of numerical hypotony did not impact the reporting of results and interpretation of glaucoma surgical studies. A new consensus to redefine hypotony failure focusing on clinically relevant complications is indicated.

The proper definition of clinical hypotony to be considered as a criterion for failure is also uncertain. Most studies incorporating hypotony sequelae as a criterion for failure also demanded a low IOP cutoff. While this is certainly an improvement over pure numerical hypotony, the presence of a cutoff may mistakenly label as a success those susceptible eyes developing potentially sight-threatening complications despite IOP values above the predefined cutoffs. In our systematic review, we found only three studies using clinical complications due to hypotony, regardless of IOP values, as a criterion for failure. One study[38] defined hypotony failure as the presence of any hypotony complications. The occurrence of a complication from hypotony indicates that a specific eye is not tolerating the specific IOP value at which the complication occurred. Therefore, specific IOP values above usual thresholds can be harmful for these eyes. Most hypotony complications, such as shallow AC or peripheral choroidal effusion, are not uncommon in the early postoperative period. These complications are typically transient and self-limiting, and while they can cause transient VA reduction, they do not usually result in permanent vision loss. Another study[18] used hypotony maculopathy to define failure. However, hypotony maculopathy as a sole criterion for hypotony failure has limitations. The prevalence of hypotony maculopathy varies depending on the method of diagnosis. Optical coherence tomography (OCT) studies have shown that subclinical maculopathy with chorioretinal undulations can be found in up to 15% of patients after trabeculectomy, with many cases undetected with fundus photography and dilated fundus examination.[39] The proportion of patients with early, non-visually significant maculopathy developing visually significant maculopathy is unknown. Additionally, peripheral macular folds distant from the foveal region may go unnoticed by the patient despite being visible on fundus examination. We argue that the use of only hypotony maculopathy is not comprehensive enough; other complications, such as suprachoroidal hemorrhage, hypotony keratopathy, and kissing choroidals, may also lead to permanent vision loss and should be regarded as a failure. A third study[40] defined failure as the occurrence of surgical revision for clinically significant hypotony. While this criterion may seem appropriate as it encompasses cases where intervention was deemed necessary due to a serious complication or non-resolving condition, some considerations should be made. The threshold for surgical intervention may vary among different surgeons. Some complications, such as suprachoroidal hemorrhage, may resolve spontaneously without intervention but could still lead to irreversible vision loss.

A clinical complication related to hypotony should be considered a criterion for failure only if it poses a substantial threat to vision and is associated with a decline in visual acuity. We propose that severe hypotony-related complications be classified as failure criteria. These include persistent large or kissing choroidals, clinically significant hypotony maculopathy, extensive suprachoroidal hemorrhage, appositional suprachoroidal hemorrhage, suprachoroidal hemorrhage associated with retinal detachment or vitreous hemorrhage, flat anterior chamber (AC) with central iridocorneal touch, hypotony keratopathy with pronounced corneal edema, or any hypotony complication necessitating revision surgery. Conversely, milder complications that either spontaneously regress without intervention or have no impact on vision should be documented but not deemed failures. Examples of these milder complications include peripheral choroidal effusion, small and peripheral suprachoroidal hemorrhage, shallow AC without central iris-corneal contact, subclinical hypotony maculopathy, hypotony keratopathy with Descemet folds and a clear cornea, and decompression retinopathy. Determining the exact impact of a specific complication on visual acuity can be challenging, especially when multiple concurrent complications or confounding factors like postoperative astigmatism and underlying ocular conditions are present. Additionally, there may be some ambiguity in defining clinical complications. For example, choroidal detachments clinically categorized as choroidal effusions may also include echographically detectable choroidal hemorrhages.

Our findings also highlight that specific hypotony criteria influence the categorization of eyes as hypotonus. This observation is consistent with a previous study conducted by Abbas and colleagues.[20] Additionally, we demonstrated that the calculated success rates of glaucoma surgery significantly varied as a function of the chosen hypotony failure criterion. In general, numerical hypotony and, to a lesser degree, mixed hypotony resulted in a higher incidence of hypotony and an elevated risk of failure compared to clinical hypotony. This outcome was not unexpected, given that only a minority of patients with numerical hypotony will encounter complications, as indicated by our study and others.[14, 15] When looking at distinct hypotony criteria, several trends emerged. The risk of failure by hypotony criteria considerably decreased when low IOP was required in two consecutive visits. For instance, the HR for the risk of such failure for criterion A was 1.97 for trabeculectomy and 1.35 for DS when the hypotony failure criterion was IOP<6 mmHg in two consecutive visits. The risk further decreases when early low IOP readings were not used to define failure. Transient numerical hypotony is common after glaucoma surgery, especially in the immediate postoperative phase, with most eyes not encountering complications. For IOP<6 mmHg in two consecutive visits after 3 months, the HR for criterion A compared to having no hypotony failure criteria was 1.35 for trabeculectomy and 1.22 for DS. While we advise against treating it as a criterion for failure, we acknowledge the value of reporting the prevalence of eyes with chronic numerical hypotony. This information provides readers with an estimate of the proportion of patients potentially at risk of hypotony complications from a specific surgical technique. Furthermore, it may be worth considering the inclusion of CCT in the definition of numerical hypotony, as CCT can influence IOP measurements. The same IOP value could imply varying risks of complications depending on the CCT.[41] However, integrating CCT into the definition of numerical hypotony is not straightforward. Formulas designed to adjust IOP readings based on CCT have been imprecise,[42] and the impact of corneal biomechanical properties on measured IOP extends beyond mere thickness. This study highlights the need for consensus and standardization in defining and reporting chronic hypotony.

This study does not provide an answer to the ultimate question of whether the use of different hypotony criteria could impact the proper interpretation of the results of a clinical study comparing the outcomes of two surgical techniques. This question is particularly relevant when comparing a highly effective technique that achieves low IOP values with less potent operations. In the 5-year results of the TVT study, 40% and 54% of failures in the trabeculectomy and tube arm, respectively, were attributed to inadequate IOP reduction;

conversely, 31% and 13% of failures in the trabeculectomy and tube arm were due to numerical hypotony. The TVT authors conducted an alternate analysis that incorporated a decrease in VA from baseline alongside their hypotony criterion. This marginally affected their estimated success rates, leaving the overall direction of the study results unchanged. However, we believe that this alternative criterion, which is essentially what we referred to as "mixed hypotony" in our study, has its limitations. A reduction in visual acuity following glaucoma surgery can be caused by factors not directly related to clinical hypotony, such as the progression of postoperative cataract or a change in astigmatism. Of note, in the TVT study, visual acuity declined over the 5-year post-intervention period for both tube and trabeculectomy patients, and this decline was comparable among patients, regardless of whether they experienced complications.[43] The frequency of hypotony complications was evenly distributed between the two arms.[43] Similar considerations may be even more relevant to the primary TVT, where the difference in success rates between the tube and trabeculectomy arms was smaller and, therefore, more susceptible to changes resulting from adopting a clinical definition of hypotony.[44, 45] This issue becomes even more pertinent when considering recent plate-less bleb-forming devices. For instance, a recent multicenter retrospective study comparing trabeculectomy and Microshunt implant outcomes, employed a numerical criterion for failure (i.e., IOP<5 mmHg in two consecutive visits after 3 months). At the 18-month mark, failure rates for trabeculectomy and Microshunt were 35% and 25%, respectively. Inadequate IOP reduction was responsible for 84% of Microshunt failures and 58% of trabeculectomy failures; in contrast, numerical hypotony accounted for 29% of trabeculectomy failures and 0% for Microshunt. The study's authors acknowledged that approximately 43% of hypotony cases were not associated with complications or a decrease in VA. Therefore, utilizing only serious hypotony-related complications as a criterion for failure would change the reported results, interpretation and clinical implications of these studies.

Trabeculectomy and DS are both well-established and effective techniques for managing glaucoma patients.[27, 46-48] The purpose of this study is not to conduct a direct comparison between different surgical techniques. Instead, the study aims to emphasize that hypotony failure criteria can impact surgical success rates in two geographically distinct study cohorts. We caution the reader not to directly compare the success rates of these two cohorts, as success rates are influenced by significantly diverse patient populations. Of note, the trabeculectomy cohort had a significantly higher prevalence of risk factors for failure, including non-white ethnicities, secondary glaucoma, low preoperative IOP values, and a history of prior glaucoma, corneal, and/or retinal surgeries. Furthermore, there may be additional differences in unobserved variables, which may only be adequately addressed within a randomized controlled trial.

In conclusion, hypotony failure criteria are highly heterogeneous in the current literature, with very few studies focusing on clinically relevant complications. Surgical success rates are considerably influenced by the hypotony criterion chosen; the use of numerical hypotony underestimates surgical success rates. The standardization of glaucoma surgical failure criteria with an emphasis on clinically relevant complications is indicated.

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During the preparation of this work the authors used chatGPT3.5 in order to improve readability and language of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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FIGURE LEGENDS

Figure 1. PRISMA flowchart illustrating the number of glaucoma studies identified and included in the analysis.

Figure 4. Kaplan-Meier curves representing the cumulative incidence of hypotony as a function of the type of hypotony (i.e., clinical, mixed, and numerical) in the trabeculectomy (left panel) and deep sclerectomy (right panel) cohorts.

Figure 5. Venn diagram illustrating the 5-year occurrence of hypotony as defined by three distinct criteria. Proportions are calculated on the entire trabeculectomy (n=934) and deep sclerectomy (n=1,765) cohort.

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Hypotony Failure Criteria in Glaucoma Surgical Studies and Their Influence on Surgery Success

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ABSTRACT

Purpose: Review hypotony failure criteria used in glaucoma surgical outcome studies and evaluate their impact on success rates.

Design: Systematic literature review and application of hypotony failure criteria to two retrospective cohorts.

Participants: 934 eyes and 1,765 eyes undergoing trabeculectomy and deep sclerectomy (DS) with a median follow-up of 41.4 and 45.4 months, respectively.

Methods: Literature-based hypotony failure criteria were applied to patient cohorts. IOP-related success was defined as: (A) IOP≤21 mmHg with ≥20% IOP reduction; (B) IOP≤18 mmHg with ≥20% reduction; (C) IOP≤15 mmHg with ≥25% reduction; (D) IOP≤12 mmHg with ≥30% reduction. Failure was defined as: IOP exceeding these criteria in two consecutive visits >3 months after surgery, loss of light perception, additional IOP-lowering surgery, or hypotony. Cox regression estimated failure risk for different hypotony criteria, using no hypotony as a reference. Analyses were conducted for each criterion and hypotony type (i.e., numerical [IOP threshold], clinical [clinical manifestations], mixed [combination of numerical and/or clinical criteria]).

Main Outcome Measures: Hazard ratio (HR) for failure risk.

Results: Of 2,503 studies found, 278 were eligible, with 99 (35.6%) studies lacking hypotony failure criteria. Numerical hypotony was predominant (157 studies [56.5%]). Few studies employed clinical hypotony (3 isolated [1.1%]; 19 combined with low IOP [6.8%]). Forty-nine different criteria were found, with IOP<6 mmHg, IOP<6 mmHg on ≥2 consecutive visits after 3 months, and IOP<5 mmHg being the most common (41 [14.7%], 38 [13.7%], and 13 [4.7%] studies, respectively). In both cohorts, numerical hypotony posed the highest risk of failure (HR between 1.51-1.21 for criteria A to D; p<0.001), followed by mixed hypotony (HR between 1.41-1.20 for criteria A to D; p<0.001), and clinical hypotony (HR between 1.12-1.04; p=0.07 for DS criteria D, p≤0.017 for other criteria). Failure risk varied greatly with various hypotony definitions, with HR ranging between 1.02-10.79 for trabeculectomy and 1.00-8.36 for DS.

Discussion: Hypotony failure criteria are highly heterogenous in the glaucoma literature, with few studies focusing on clinical manifestations. Numerical hypotony yields higher failure rates than clinical hypotony and can underestimate glaucoma surgery success rates. Standardizing failure criteria with an emphasis on clinically relevant hypotony manifestations is needed.

Keywords: antimetabolites; choroidal effusion; glaucoma surgery; hypotony maculopathy; intraocular pressure; nonpenetrating glaucoma surgery; post-operative complications; randomized controlled study; retrospective study; trabeculectomy.

INTRODUCTION

Intraocular pressure (IOP) reduction is currently the only proven treatment to slow the progression of glaucoma, and it is achieved through medical, laser, and surgical treatments.[1] Glaucoma surgery has been traditionally reserved for eyes with uncontrolled disease despite medical and laser therapies. Previous studies have shown that glaucoma surgery effectively lowers IOP and reduces glaucomatous progression rates.[2, 3] Glaucoma surgery can provide a robust and sustained reduction in IOP, prevent further glaucoma deterioration, and preserve vision-related quality of life.

Postoperative hypotony can occur as a result of glaucoma surgery. The definition of hypotony varies in the literature and is usually categorized as numerical or clinical. Numerical hypotony is defined as an IOP below a certain threshold that is considered non-physiological and carries a risk of severe complications.[4] Clinical hypotony focuses more on the presence of complications caused by low IOP, regardless of the IOP reading. Some of these complications (e.g., hypotony maculopathy, choroidal hemorrhage) may be particularly serious and lead to irreversible loss of vision.[5, 6]

To standardize glaucoma surgery studies, the World Glaucoma Association (WGA) has issued guidelines for designing and reporting glaucoma surgical studies.[7] These guidelines recommend persistent numerical hypotony (i.e., IOP <6 mmHg for two consecutive examinations) as one of the failure criteria. Following WGA guidelines, persistent hypotony was set as a criterion for failure in many studies, including landmark surgical studies.[8-12] However, recent studies have questioned whether simple numerical hypotony truly reflects surgical outcomes.[13, 14] Most eyes with low IOP do not develop complications,[14, 15] and their outcomes are not significantly different from those without hypotony in terms of visual acuity, reoperation rates, and surgical failure.[13, 14] Additionally, patients with predisposing factors may experience sight-threatening hypotony complications even in the absence of numerical hypotony.[14, 15] Therefore, the widespread use of numerical hypotony as a failure criterion seems inappropriate, as it can misclassify successful operations as surgical failures and vice versa. Few studies[16-19] have adopted alternative definitions of hypotony failure based on the presence of hypotony complications alone or in combination with a low IOP cutoff.

The lack of consistency in defining failure criteria due to hypotony increases the heterogeneity of the literature, making it difficult to compare results from different studies. Abbas and colleagues[20] conducted a study evaluating how fourteen different hypotony failure definitions affected the proportion of patients labeled as having hypotony, and they found wide variations in hypotony prevalence depending on the criterion used. The impact of using different hypotony criteria for failure on success rates of glaucoma surgery is still unknown. The use of numerical criteria, such as the one proposed by the WGA guidelines, may disproportionately penalize techniques that can achieve a more substantial reduction in IOP (e.g., trabeculectomy) compared to less potent surgeries (e.g., plate-less bleb-forming devices, aqueous shunts).

In this study, we systematically review hypotony definitions used in the literature and assess the impact of different hypotony failure criteria on glaucoma surgery success rates in two large cohorts of patients undergoing trabeculectomy and deep sclerectomy (DS) with long-term follow-up.

METHODS

Publication Search and Assessment

We conducted a systematic literature review (PROSPERO CRD42022378096) in PubMed using the following search terms: Ahmed valve, Baerveldt, deep sclerectomy, express shunt, glaucoma drainage device, glaucoma operation, glaucoma surgery, glaucoma tube, glaucoma valve, Innfocus, Preserflo Microshunt, Trabeculectomy, Xen gel stent, Xen implant, Xen Stent. We limited the results to clinical studies, clinical trials (all types), comparative studies, multicenter studies, and observational studies. We included articles published in English on human patients from January 1, 2010 to November 21, 2022. This time frame encompassed studies published within a year after the introduction of the World Glaucoma Association (WGA) consensus document on reporting glaucoma surgical studies up to the design of our study.[7] We included studies that reported success rates of glaucoma surgical procedures performed alone or in conjunction with other ocular surgeries (e.g., cataract surgery). We included surgical techniques that provided subconjunctival filtration, either *ab externo* (e.g., trabeculectomy, glaucoma drainage devices, deep sclerectomy, Preserflo MicroShunt, Express shunt) or *ab interno* (e.g., Xen Gel). We excluded other surgeries targeting the trabecular meshwork and suprachoroidal space as these techniques have different indications, IOP-lowering efficacy, and rarely lead to hypotony. We did not include studies on glaucoma laser procedures or medications for the same reasons. If a study compared different surgical techniques, it was included as long as at least one of the study procedures met our inclusion criteria. We used the Rayyan web application[21] to screen titles and abstracts of potentially eligible studies. Prior to data screening, we removed studies with duplicated information or those not primarily written in English.

Two independent investigators (AR and GT) screened the titles and abstracts to select studies for full-text review. The reviewers were masked to each other's decisions until the study selection was completed. Disagreement was resolved with open adjudication between the two investigators. If no agreement could be reached, a third investigator was involved to make the final decision. For those studies that passed the screening process, we obtained the full text through PubMed, journal website or other sources. If articles could not be found, we contacted the corresponding authors to request a copy. If there was no response from the corresponding author within four weeks, the article was excluded from the full-text review.

The same two investigators independently extracted relevant information, including the specific definition of hypotony used as a failure criterion and the type of hypotony. The type of hypotony was classified as numerical (based on intraocular pressure thresholds only), clinical (based on clinical manifestations of hypotony only), or mixed (a combination of numerical and/or clinical criteria).

The reviewers were masked to each other's decisions until the data extraction was completed. Disagreements were resolved through open adjudication between the two investigators. If an agreement could not be reached, a third investigator was involved to make the final decision.

Patients' cohorts

Two large retrospective clinical datasets of patients undergoing either trabeculectomy or nonpenetrating deep sclerectomy were included.

The trabeculectomy dataset included patients who underwent trabeculectomy between 1999 and 2022 at the Glaucoma Division of the Stein Eye Institute, University of California, Los Angeles. Surgeries were performed or supervised by one of the five attendings using a previously reported technique.[22-24] The use of this dataset was approved by the institution review board (IRB) at the University of California, Los Angeles and adhered with the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. The IRB waived the requirement for written informed consent.

The deep sclerectomy dataset consisted of consecutive patients who underwent deep sclerectomy in two UK glaucoma services: Calderdale and Huddersfield NHS Foundation Trust (between 2001 and 2014) and Gloucestershire Hospitals NHS Foundation

Trust (between 2014 and 2020). The patients were under the care of a single glaucoma and anterior segment surgeon (NA). All data were fully anonymized prior to analysis. The surgical procedures were either performed or supervised by an experienced glaucoma surgeon (NA) and followed a standardized technique described in previous publications.[14, 25-27] This study did not directly involve human subjects, identifiable human material, or identifiable data. According to UK legislation, the use of a retrospective dataset for anonymized database analyses is considered an audit or service evaluation and does not require IRB approval. The study adhered to the principles outlined in the Declaration of Helsinki, the United Kingdom Data Protection Act, and the National Institute for Health Research guidance. The retrospective anonymized data extraction was approved by the Calderdale and Huddersfield NHS Foundation Trust and the Gloucestershire Hospitals NHS Caldicott Guardians, who are responsible for information governance.

From the two datasets, we used the following preoperative variables for the analysis: eye and patient identification numbers, age, ethnicity, laterality, central corneal thickness (CCT), Snellen best-corrected visual acuity (BCVA), IOP measured with Goldmann applanation tonometry, number of topical antiglaucoma agents, use of systemic acetazolamide, visual field mean deviation (MD), glaucoma subtype, lens status, previous laser trabeculoplasty, previous glaucoma, lens, corneal, and retinal surgery and their type. Intraoperative variables included whether the trabeculectomy or DS was performed stand-alone or combined with other ocular procedures. Postoperative variables were collected for any available visit and included: IOP, BCVA, postoperative complications occurrence, their type and their grade (where available), revision surgery and its reasons (e.g., hypotony, dystesthesia), other subsequent glaucoma surgery or ciliodestructive procedure. If an eye underwent further glaucoma surgery, we censored its follow-up at the time of the listing visit. We included both eyes of the same patient if eligible. If the same eye underwent two or more glaucoma surgery in the study period, we included the first available surgery. We excluded eyes in which preoperative IOP and BCVA were not available as this prevented the calculation of success rates. No other inclusion/exclusion criteria were applied.

Criteria for success

Four different upper IOP cutoff were chosen as criteria for success: (A) IOP≤21 mmHg with ≥20% IOP reduction from preoperative values; (B) IOP≤18 mmHg with ≥20% IOP reduction; (C) IOP≤15 mmHg with ≥25% IOP reduction; (D) IOP≤12 mmHg with ≥30% IOP reduction. Failure was defined as follows: IOP above the specified criteria in two consecutive visits three months after surgery, loss of light perception, additional IOP-lowering glaucoma surgery or ciliodestructive procedures, and hypotony. We applied each of the different hypotony criteria identified in the systematic review to the patient cohort sequentially. For each dataset, we calculated multiple success rates corresponding to the different hypotony criteria identified in the literature that were replicable. By keeping the first three failure criteria fixed and varying only the definition of hypotony, we were able to evaluate the impact of different hypotony failure criteria. Hypotony complications were defined as the presence of one or more of the following: reduced AC depth with any degree of iris-corneal touch, hypotony maculopathy, choroidal effusion, choroidal hemorrhage, hypotony keratopathy, and decompression retinopathy.

Statistical Analysis

Statistical analysis was performed with the open-source software R (R Foundation for Statistical Computing, Vienna, Austria). All tests were 2-tailed, and p-values <0.05 were considered statistically significant. We converted Snellen visual acuity values to the logarithm of the minimum angle of resolution (logMAR) scale. Continuous variables were reported as mean (± standard deviation [SD]) or median (interquartile range [IQR]), and categorical variables as frequencies or proportions.

Differences in demographic and preoperative variables between the two cohorts were tested. Differences in patient-related categorical variables (e.g., ethnicity) were tested with the chi square test. Differences in eye-related variables (e.g., BCVA, IOP) were tested with a mixed model, where the patient identification number was included as a random effect to account for the inclusion of the two eyes from the same patients. We used linear mixed models (package *lme4*)[28] and generalized mixed models with adaptive Gaussian quadrature (package *GLMMadaptive*)[29] for continuous and categorical variables, respectively. Multinomial categorical variables, such as type of glaucoma, baseline lens status, and surgical procedure, were binarized using the most prevalent category as the reference level.

We used Kaplan-Meir survival curves to calculate the overall cumulative incidence of hypotony and success based on the various IOP criteria. We clustered data for the patient identification number to account for the inclusion of two eyes of the same patient, and a robust variance estimate based on the infinitesimal jackknife estimate was used to calculate unbiased standard errors.[30] We conducted analyses separately for each criterion and type of hypotony (i.e., numerical, clinical, mixed). We generated Venn diagrams to visualize the relationships between clinical hypotony and hypotony failure criteria most commonly reported in the literature. We calculated the sensitivity and specificity of each numerical criterion to diagnose the presence of hypotony complications. We ran clustered Cox regression analyses with robust variance estimation (to account for within-data correlations) to test differences between groups and estimate the risk of failure according to the various criteria when having no hypotony failure criterion as a reference. We employed the Tukey method for pairwise comparison.

RESULTS

Systematic Review

We initially identified 2,503 studies through the database search (Figure 1). After excluding 201 studies with duplicate information and 24 studies not in English, we screened 2,278 unique abstracts. Among these, 291 abstracts met the eligibility criteria and underwent full-text review. From the eligible studies, thirteen studies were further excluded due to reasons such as duplicated information (n=6), unavailability of full text (n=3), absence of reported success rates (n=2), cross-sectional design (n=1), and the use of a suprachoroidal device (n=1). Hypotony failure definitions were extracted from the remaining 278 articles.

Out of the included studies, 99 (35.6%) did not use any hypotony failure criteria. Numerical hypotony was the most commonly adopted failure criterion, present in 157 studies (56.5%). Only a small number of studies incorporated clinical complications of hypotony as failure criteria, either in isolation (3 studies [1.1%]) or in combination with a low IOP cutoff (19 studies [6.8%]). When the prevalence of hypotony failure criteria was stratified as a function of the year of publication (Figure S2), the proportion of studies with no hypotony failing criteria progressively decreased from 61.5% in 2010 to 8.3% in 2022. Conversely, the proportion of studies using numerical hypotony progressively increased from 30.8% in 2010 to 75% in 2022. The use of mixed hypotony and clinical hypotony was inconsistent and did not follow any trend.

Figure S3 illustrates that a total of forty-nine specific hypotony failure criteria were identified, with IOP<6 mmHg, IOP<6 mmHg on ≥2 consecutive visits after 3 months from surgery, and IOP<5 mmHg being the most frequently used failure criteria in 41 (14.7%), 38 (13.7%), and 13 (4.7%) studies, respectively. One of the 49 hypotony failure criteria (i.e., sustained IOP<5 mmHg)[31, 32] could not be applied to our patient cohorts as the authors did not provide enough details to make them replicable, particularly with regards to the period of time required to define hypotony as “sustained”.

Patient Cohorts

A total of 934 eyes of 766 patients and 1,765 eyes of 1,385 patients were included in the trabeculectomy and deep sclerectomy cohorts, respectively. The median (IQR) follow-up was 41.4 (19.3 – 74.8) months and 45.4 (20.9 – 79.8) months in the trabeculectomy and DS cohort, respectively. Table 1 illustrates the demographic and clinical characteristics of the included patients.

Hypotony incidence

Figure 4 illustrates the cumulative incidence of hypotony in the two patient cohorts. In both cohorts, numerical hypotony (i.e., intraocular pressure thresholds only) had the highest cumulative incidence, followed by mixed hypotony (i.e., a combination of numerical and/or clinical criteria), and clinical hypotony (i.e., clinical manifestations of hypotony only). Differences in hypotony incidence, as estimated with different hypotony types, were statistically significant for all pairwise comparisons ($p<0.001$).

With regards to the specific hypotony criteria (Table S2), the median (IQR) 5-year estimated incidence (95% CI) of hypotony was 18.9% (11.3%-30.2%) and 8.0% (5.1%-16.8%) for the trabeculectomy and DS, respectively. Among the three most commonly used criteria in the literature (Table 3), IOP<6 mmHg led to the highest estimated 5-year incidence of hypotony, followed by IOP<5 mmHg, and, considerably lower, IOP<6 mmHg on ≥2 consecutive visits after 3 months from surgery. Among clinical hypotony criteria, the use of hypotony complications led to the highest estimated 5-year incidence of hypotony, followed by hypotony maculopathy, and surgical reoperation for hypotony. As shown in Figure 5, a sizable proportion of patients categorized as “failed” due to hypotony with the two most used criteria (i.e., IOP<6 mmHg, IOP<6 mmHg on ≥2 consecutive visits after 3 months) did not experience any clinical complication. Conversely, only 4 (0.4%) and 5 (0.3%) patients in the trabeculectomy and DS cohorts, respectively, developed complications despite not meeting these numerical hypotony thresholds. Table 4 presents the sensitivity and specificity values of each numerical hypotony criterion for identifying clinical complications. No specific criterion demonstrated strong diagnostic properties. In general, criteria that did not impose any time cutoff from the original surgery and did not require confirmation of IOP readings in subsequent visits tended to have higher sensitivity but lower specificity. This suggests that they were more likely to detect hypotony complications but also had a higher rate of false positives. Conversely, criteria that included a time cutoff from surgery and required low IOP in multiple visits or at the last visit tended to have higher specificity but lower sensitivity. These criteria were more precise in confirming hypotony complications but might miss early or transient hypotony complications.

Surgical success rates by hypotony type

Figure S6 and Table S5 illustrate the success rates of the two surgical procedures as a function of the type of hypotony. The 5-year success rates for trabeculectomy and DS were highest with no hypotony failure criteria (criteria A-D: trabeculectomy 40.9-23.2%; DS: 62.4-15.0%), followed by clinical hypotony (criteria A-D: trabeculectomy 37.9-21.5%; DS: 59.7-13.8%), mixed hypotony (criteria A-D: trabeculectomy 31.7-16.7%; DS: 54.2-11.7%), and numerical hypotony (criteria A-D: trabeculectomy 28.3-13.7%; DS: 52.6-11.0%).

Figure S7 and Table S6 illustrate the results of the Cox regression analysis based on the hypotony type compared to having no hypotony failure criteria. In both cohorts, numerical hypotony posed the highest risk of labeling a patient as a failure (trabeculectomy HR between 1.51-1.41 for criteria A to D; $p<0.001$; DS HR between 1.46-1.21 for criteria A to D; $p<0.001$), followed by mixed hypotony (trabeculectomy HR between 1.40-1.31 for criteria A to D; $p<0.001$; DS HR between 1.41-1.20 for criteria A to D; $p<0.001$), and clinical hypotony (trabeculectomy HR between 1.12-1.09 for criteria A to D; $p<0.001$; DS HR between 1.10-1.04 for criteria A to D; $p<0.001$). The impact of different hypotony criteria was considerably reduced with more stringent IOP upper cutoffs in the DS cohort, while it only slightly decreased in the trabeculectomy cohort.

Surgical success rates by specific hypotony criteria

As shown in Figure S8 and Tables S7 and S8, estimated success rates varied greatly as a function of the specific hypotony criterion chosen. Among the three most commonly used criteria in the literature (Table 9), IOP<6 mmHg on ≥2 consecutive visits after 3 months from surgery led to the highest 5-year success rates for all criteria, followed by IOP<5 mmHg, and IOP<6 mmHg. Regarding clinical hypotony (Table 9), the 5-year success rates were the highest using the presence of hypotony maculopathy, followed by surgical revision for hypotony, and hypotony complications.

Figure S9 and Tables S10 and S11 detail the risk of failure using the various individual criteria having no hypotony failure criteria as a reference in the two cohorts of patients. Among the three most commonly used criteria, IOP<6 mmHg led to the highest risk of failure, followed by IOP<5 mmHg, and IOP<6 mmHg on ≥2 consecutive visits after 3 months from surgery. When looking at clinical hypotony criteria, hypotony complications were significantly ($p<0.001$) associated with an increased risk of failure. Using hypotony maculopathy or revision for hypotony complications marginally increased the risk of failure compared to having no hypotony failure criteria.

DISCUSSION

In this study, we conducted a systematic literature review to identify the definitions of hypotony used as failure criteria in glaucoma surgical outcome studies. We then applied the identified criteria to two large cohorts of patients undergoing trabeculectomy and DS surgery. We found that hypotony failure criteria were highly heterogeneous in the current literature, with 49 distinct criteria identified. Additionally, most studies either lacked hypotony failure criteria altogether or relied on numerical cutoffs, and only a few studies focused on clinically relevant hypotony manifestations. When we applied the various hypotony criteria to our two patient cohorts, we observed a substantial impact on the incidence of hypotony and the success rates. The choice of hypotony criterion significantly influenced the results, with the use of numerical hypotony only leading to a likely underestimation of true surgical success rates. This result is particularly meaningful given the long follow-up time, which would have allowed us to detect clinically significant consequences of hypotony.

The goal of any glaucoma treatment is to slow glaucoma progression, preventing visual disability and loss of vision-related quality of life. As such, the use of visual field and its progression rates as a primary outcome for surgical success has been advocated.[33, 34] However, visual field progression has been infrequently used as a primary outcome in glaucoma surgical studies. Despite being an imperfect surrogate measure for disease progression, IOP control has been routinely used to gauge the success of surgical techniques. Historical studies, however, were highly heterogeneous in defining tonometric success, and the specific set of criteria used to define IOP control influenced estimated success rates.[35] Historical literature gave little emphasis to hypotony, with most studies having no hypotony criteria.[35] In 2009, the World Glaucoma Association (WGA) released a consensus document on designing and reporting glaucoma surgical studies to provide some standardization.[7] The WGA consensus introduced a numerical hypotony criterion for failure, defining failure as an IOP<6 mmHg (preferably on two consecutive visits). The tube-versus-trabeculectomy (TVT) study[36] chose to adopt variations of the WGA hypotony criteria, introducing a window of three months from the original surgery to overcome the impact of early hypotony. Early hypotony may be relatively frequent after glaucoma surgery, and the IOP behavior in the early postoperative visits may not reflect long-term IOP control. As a consequence of the WGA guidelines and study design of milestone studies, the number of studies incorporating some form of hypotony failure criteria progressively increased over time, with fewer than one in ten studies lacking such criteria in 2022. Our work also revealed that the heterogeneity in hypotony failure criteria remains very high in the current literature, with approximately one diverse criterion in every five published studies. One-third of the studies used an IOP threshold similar to those recommended by the WGA (IOP<6 mmHg or IOP≤6 mmHg) or the TVT study. This finding, in conjunction with the progressive incorporation of hypotony failure criteria, confirms that consensus documents and milestone studies have the potential to impact research methods and the clinical care of glaucoma.

Although the use of a numerical cutoff is simple and convenient, recent studies[13, 14] have shown that numerical hypotony is a poor surrogate for the presence of clinically significant hypotony. In our study (Figure 5), most patients with numerical hypotony did not develop any complications. Conversely, approximately 0.3-0.4% of patients with no numerical hypotony experienced hypotony complications. This finding aligns with previous studies indicating higher risk of complication, such as hypotony maculopathy, choroidal hemorrhage, or choroidal effusion, in certain patient categories. These include young patients with more elastic sclera, myopes with thinner sclera, and vitrectomized patients lacking vitreous body support for the sclera.[14, 15, 37] In these patients, hypotony complications may occur at IOP values considered 'normal' by a numerical definition of hypotony. Therefore, numerical hypotony is neither sufficient nor necessary to develop hypotony complications. We found that the use of clinical hypotony as a criterion for failure is very uncommon, with no evident increasing trend in recent years. This suggests that recent articles pointing out the fallacy of numerical hypotony did not impact the reporting of results and interpretation of glaucoma surgical studies. A new consensus to redefine hypotony failure focusing on clinically relevant complications is indicated.

The proper definition of clinical hypotony to be considered as a criterion for failure is also uncertain. Most studies incorporating hypotony sequelae as a criterion for failure also demanded a low IOP cutoff. While this is certainly an improvement over pure numerical hypotony, the presence of a cutoff may mistakenly label as a success those susceptible eyes developing potentially sight-threatening complications despite IOP values above the predefined cutoffs. In our systematic review, we found only three studies using clinical complications due to hypotony, regardless of IOP values, as a criterion for failure. One study[38] defined hypotony failure as the presence of any hypotony complications. The occurrence of a complication from hypotony indicates that a specific eye is not tolerating the specific IOP value at which the complication occurred. Therefore, specific IOP values above usual thresholds can be harmful for these eyes. Most hypotony complications, such as shallow AC or peripheral choroidal effusion, are not uncommon in the early postoperative period. These complications are typically transient and self-limiting, and while they can cause transient VA reduction, they do not usually result in permanent vision loss. Another study[18] used hypotony maculopathy to define failure. However, hypotony maculopathy as a sole criterion for hypotony failure has limitations. The prevalence of hypotony maculopathy varies depending on the method of diagnosis. Optical coherence tomography (OCT) studies have shown that subclinical maculopathy with chorioretinal undulations can be found in up to 15% of patients after trabeculectomy, with many cases undetected with fundus photography and dilated fundus examination.[39] The proportion of patients with early, non-visually significant maculopathy developing visually significant maculopathy is unknown. Additionally, peripheral macular folds distant from the foveal region may go unnoticed by the patient despite being visible on fundus examination. We argue that the use of only hypotony maculopathy is not comprehensive enough; other complications, such as suprachoroidal hemorrhage, hypotony keratopathy, and kissing choroidals, may also lead to permanent vision loss and should be regarded as a failure. A third study[40] defined failure as the occurrence of surgical revision for clinically significant hypotony. While this criterion may seem appropriate as it encompasses cases where intervention was deemed necessary due to a serious complication or non-resolving condition, some considerations should be made. The threshold for surgical intervention may vary among different surgeons. Some complications, such as suprachoroidal hemorrhage, may resolve spontaneously without intervention but could still lead to irreversible vision loss.

A clinical complication related to hypotony should be considered a criterion for failure only if it poses a substantial threat to vision and is associated with a decline in visual acuity. We propose that severe hypotony-related complications be classified as failure criteria. These include persistent large or kissing choroidals, clinically significant hypotony maculopathy, extensive suprachoroidal hemorrhage, appositional suprachoroidal hemorrhage, suprachoroidal hemorrhage associated with retinal detachment or vitreous hemorrhage, flat anterior chamber (AC) with central iridocorneal touch, hypotony keratopathy with pronounced corneal edema, or any hypotony complication necessitating revision surgery. Conversely, milder complications that either spontaneously regress without intervention or have no impact on vision should be documented but not deemed failures. Examples of these milder complications include peripheral choroidal effusion, small and peripheral suprachoroidal hemorrhage, shallow AC without central iris-corneal contact, subclinical hypotony maculopathy, hypotony keratopathy with Descemet folds and a clear cornea, and decompression retinopathy. Determining the exact impact of a specific complication on visual acuity can be challenging, especially when multiple concurrent complications or confounding factors like postoperative astigmatism and underlying ocular conditions are present. Additionally, there may be some ambiguity in defining clinical complications. For example, choroidal detachments clinically categorized as choroidal effusions may also include echographically detectable choroidal hemorrhages.

Our findings also highlight that specific hypotony criteria influence the categorization of eyes as hypotonus. This observation is consistent with a previous study conducted by Abbas and colleagues.[20] Additionally, we demonstrated that the calculated success rates of glaucoma surgery significantly varied as a function of the chosen hypotony failure criterion. In general, numerical hypotony and, to a lesser degree, mixed hypotony resulted in a higher incidence of hypotony and an elevated risk of failure compared to clinical hypotony. This outcome was not unexpected, given that only a minority of patients with numerical hypotony will encounter complications, as indicated by our study and others.[14, 15] When looking at distinct hypotony criteria, several trends emerged. The risk of failure by hypotony criteria considerably decreased when low IOP was required in two consecutive visits. For instance, the HR for the risk of such failure for criterion A was 1.97 for trabeculectomy and 1.35 for DS when the hypotony failure criterion was IOP<6 mmHg in two consecutive visits. The risk further decreases when early low IOP readings were not used to define failure. Transient numerical hypotony is common after glaucoma surgery, especially in the immediate postoperative phase, with most eyes not encountering complications. For IOP<6 mmHg in two consecutive visits after 3 months, the HR for criterion A compared to having no hypotony failure criteria was 1.35 for trabeculectomy and 1.22 for DS. While we advise against treating it as a criterion for failure, we acknowledge the value of reporting the prevalence of eyes with chronic numerical hypotony. This information provides readers with an estimate of the proportion of patients potentially at risk of hypotony complications from a specific surgical technique. Furthermore, it may be worth considering the inclusion of CCT in the definition of numerical hypotony, as CCT can influence IOP measurements. The same IOP value could imply varying risks of complications depending on the CCT.[41] However, integrating CCT into the definition of numerical hypotony is not straightforward. Formulas designed to adjust IOP readings based on CCT have been imprecise,[42] and the impact of corneal biomechanical properties on measured IOP extends beyond mere thickness. This study highlights the need for consensus and standardization in defining and reporting chronic hypotony.

This study does not provide an answer to the ultimate question of whether the use of different hypotony criteria could impact the proper interpretation of the results of a clinical study comparing the outcomes of two surgical techniques. This question is particularly relevant when comparing a highly effective technique that achieves low IOP values with less potent operations. In the 5-year results of the TVT study, 40% and 54% of failures in the trabeculectomy and tube arm, respectively, were attributed to inadequate IOP reduction;

conversely, 31% and 13% of failures in the trabeculectomy and tube arm were due to numerical hypotony. The TVT authors conducted an alternate analysis that incorporated a decrease in VA from baseline alongside their hypotony criterion. This marginally affected their estimated success rates, leaving the overall direction of the study results unchanged. However, we believe that this alternative criterion, which is essentially what we referred to as "mixed hypotony" in our study, has its limitations. A reduction in visual acuity following glaucoma surgery can be caused by factors not directly related to clinical hypotony, such as the progression of postoperative cataract or a change in astigmatism. Of note, in the TVT study, visual acuity declined over the 5-year post-intervention period for both tube and trabeculectomy patients, and this decline was comparable among patients, regardless of whether they experienced complications.[43] The frequency of hypotony complications was evenly distributed between the two arms.[43] Similar considerations may be even more relevant to the primary TVT, where the difference in success rates between the tube and trabeculectomy arms was smaller and, therefore, more susceptible to changes resulting from adopting a clinical definition of hypotony.[44, 45] This issue becomes even more pertinent when considering recent plate-less bleb-forming devices. For instance, a recent multicenter retrospective study comparing trabeculectomy and Microshunt implant outcomes, employed a numerical criterion for failure (i.e., IOP<5 mmHg in two consecutive visits after 3 months). At the 18-month mark, failure rates for trabeculectomy and Microshunt were 35% and 25%, respectively. Inadequate IOP reduction was responsible for 84% of Microshunt failures and 58% of trabeculectomy failures; in contrast, numerical hypotony accounted for 29% of trabeculectomy failures and 0% for Microshunt. The study's authors acknowledged that approximately 43% of hypotony cases were not associated with complications or a decrease in VA. Therefore, utilizing only serious hypotony-related complications as a criterion for failure would change the reported results, interpretation and clinical implications of these studies.

Trabeculectomy and DS are both well-established and effective techniques for managing glaucoma patients.[27, 46-48] The purpose of this study is not to conduct a direct comparison between different surgical techniques. Instead, the study aims to emphasize that hypotony failure criteria can impact surgical success rates in two geographically distinct study cohorts. We caution the reader not to directly compare the success rates of these two cohorts, as success rates are influenced by significantly diverse patient populations. Of note, the trabeculectomy cohort had a significantly higher prevalence of risk factors for failure, including non-white ethnicities, secondary glaucoma, low preoperative IOP values, and a history of prior glaucoma, corneal, and/or retinal surgeries. Furthermore, there may be additional differences in unobserved variables, which may only be adequately addressed within a randomized controlled trial.

In conclusion, hypotony failure criteria are highly heterogeneous in the current literature, with very few studies focusing on clinically relevant complications. Surgical success rates are considerably influenced by the hypotony criterion chosen; the use of numerical hypotony underestimates surgical success rates. The standardization of glaucoma surgical failure criteria with an emphasis on clinically relevant complications is indicated.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used chatGPT3.5 in order to improve readability and language of the manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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FIGURE LEGENDS

Figure 1. PRISMA flowchart illustrating the number of glaucoma studies identified and included in the analysis.

Figure 4. Kaplan-Meier curves representing the cumulative incidence of hypotony as a function of the type of hypotony (i.e., clinical, mixed, and numerical) in the trabeculectomy (left panel) and deep sclerectomy (right panel) cohorts.

Figure 5. Venn diagram illustrating the 5-year occurrence of hypotony as defined by three distinct criteria. Proportions are calculated on the entire trabeculectomy (n=934) and deep sclerectomy (n=1,765) cohort.

Figure 1

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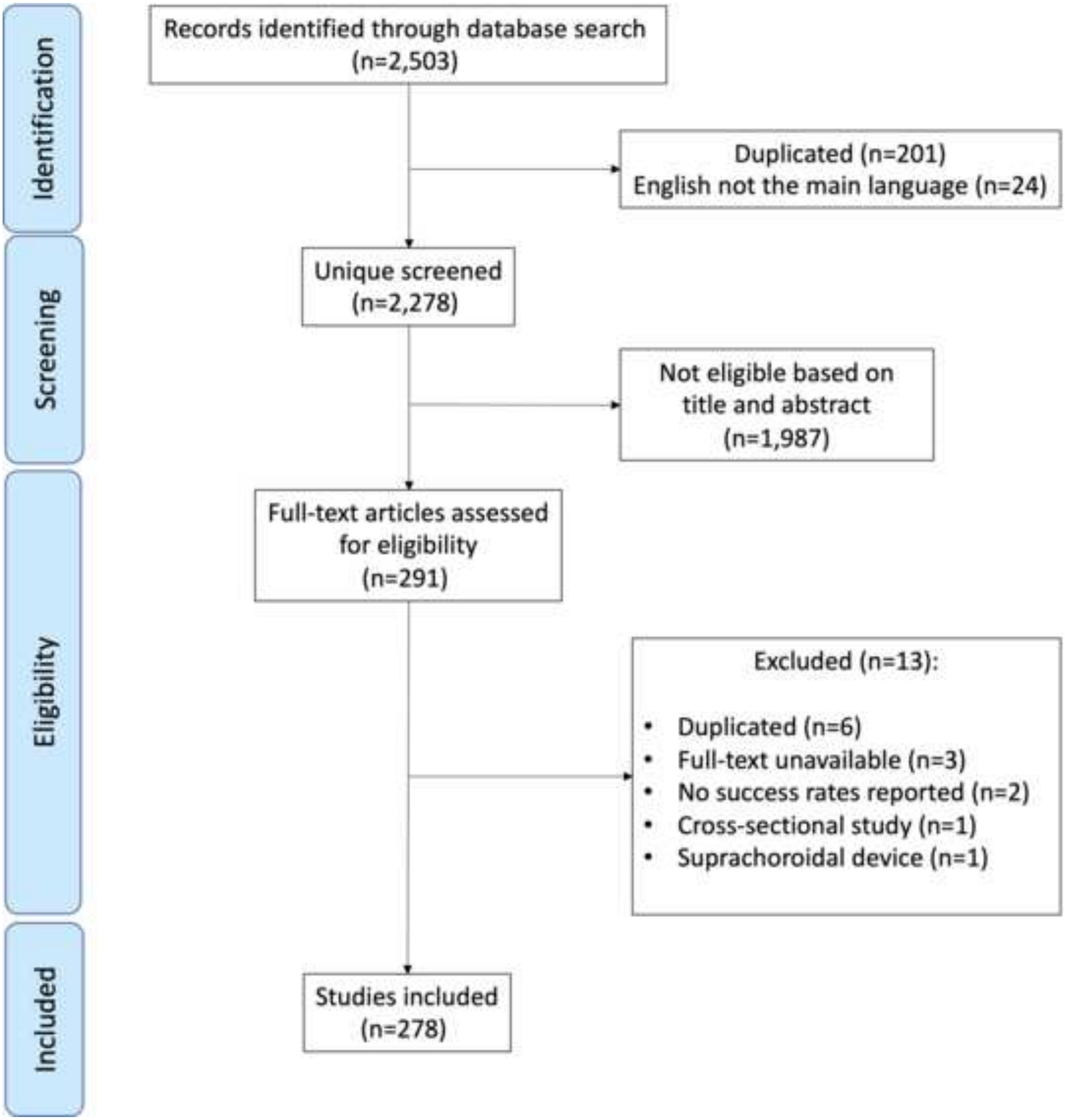

Figure 4

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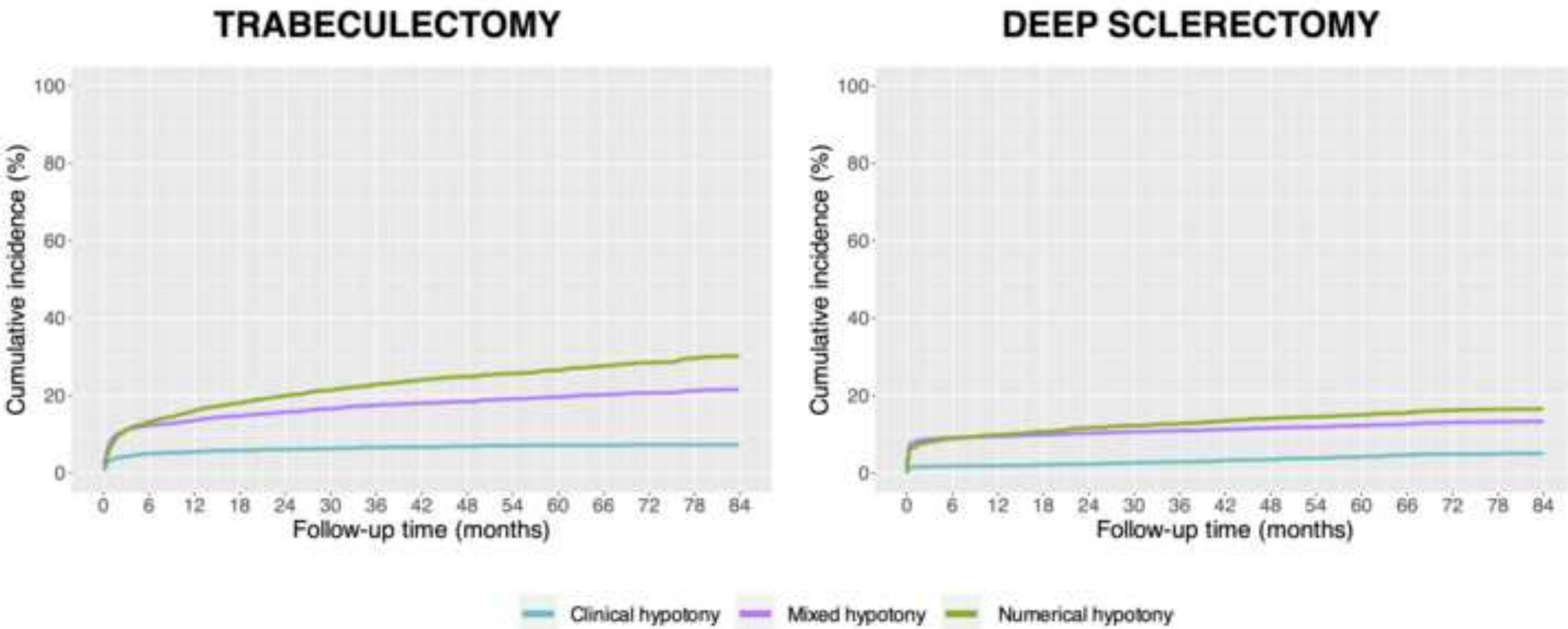

Figure 5

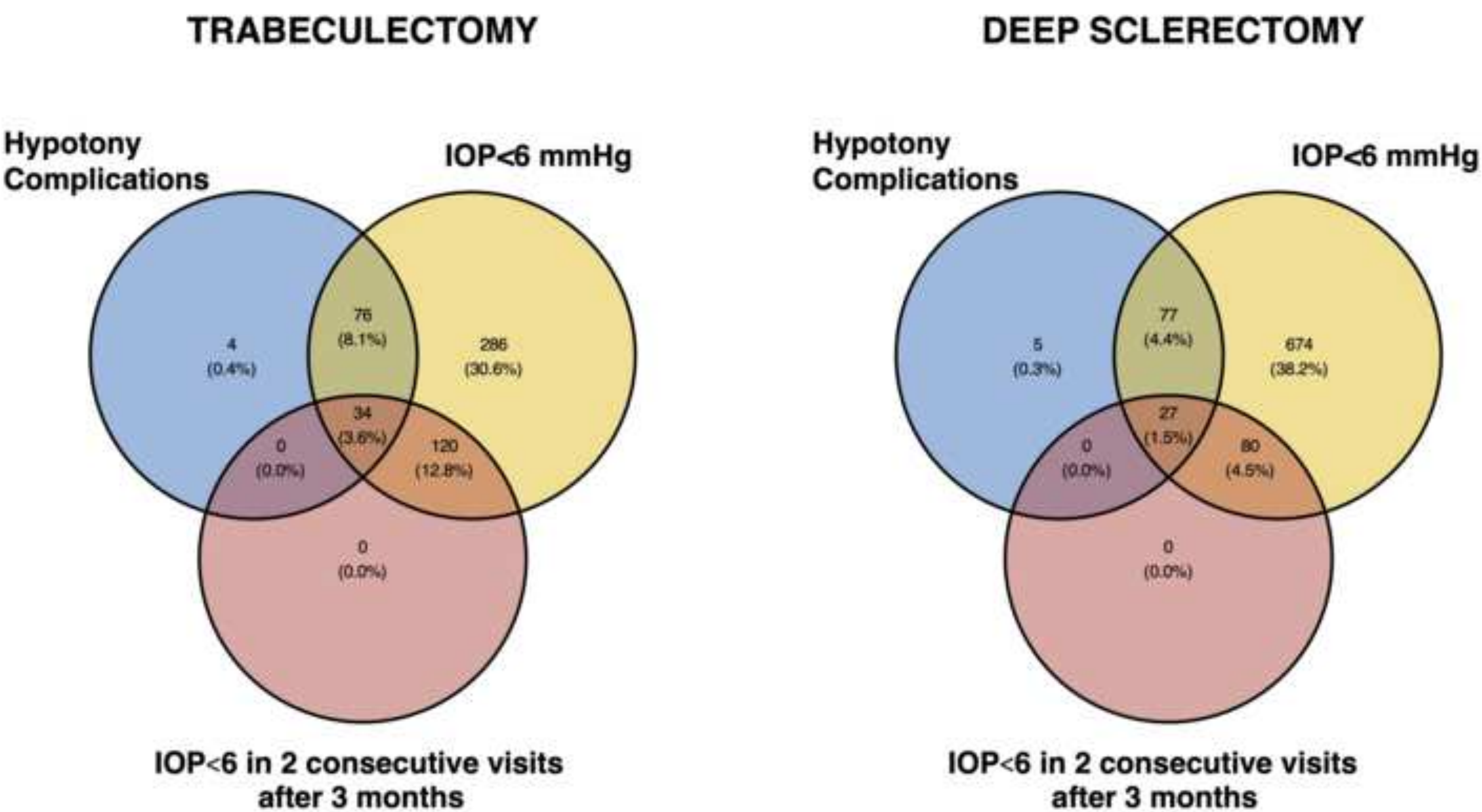
TRABECULECTOMY
Hypotony Complications
IOP<6 mmHg
4 (0.4%)
76 (8.1%)
286 (30.6%)
34 (3.6%)
0 (0.0%)
120 (12.8%)
0 (0.0%)
IOP<6 in 2 consecutive visits after 3 months
DEEP SCLERECTOMY
Hypotony Complications
IOP<6 mmHg
5 (0.3%)
77 (4.4%)
674 (38.2%)
27 (1.5%)
0 (0.0%)
80 (4.5%)
0 (0.0%)
IOP<6 in 2 consecutive visits after 3 months

Table 1. Demographic and clinical characteristics of included patients.

	Trabeculectomy	DS	p-value
No. Eyes/Patients	934 / 766	1765 / 1385	
Age, years, mean ± SD	74.4 ± 10.6	73.1 ± 12.4	**0.009**
Race and Ethnicity, n (%)			**<0.001**
Asian	104 (13.6%)	29 (2.1%)	
Black	90 (11.8%)	28 (2.0%)	
Latino~~White~~	73 (9.5%)~~432 (56.4%)~~	0 (0%)~~1327 (95.8%)~~	
White ~~Asian~~	432 (56.4%)~~104 (13.6%)~~	1327 (95.8%)~~29 (2.1%)~~	
Other	37 (4.8%)	1 (0.1%)	
Unknown	30 (3.9%)	0 (0%)	
Gender, female (%)	431 (56.3%)	696 (50.3%)	**<0.001**
Eye, right / left	472 / 462	879 / 886	0.68
CCT, µm, mean ± SD	542 ± 44	527 ± 40	**<0.001**
Baseline BCVA, logMAR, median (IQR)	0.2 (0.4 – 0.10)	0.2 (0.0 – 0.5)	0.91
Baseline IOP, mmHg, median (IQR)	17 (13 – 23)	22 (19 – 26)	**<0.001**
Baseline MD, dB, median (IQR)	-12.5 (- 6.2 to -19.3)	-10.7 (-5.6 to -17.2)	0.20
Number of glaucoma topical agents, median (IQR)	3 (3 – 4)	2 (2 – 3)	**<0.001**
Systemic acetazolamide, no eyes (%)	102 (10.9%)	44 (2.5%)	**<0.001**

Glaucoma type, no eyes (%)			**<0.001**
POAG/NTG	642 (68.7%)	1,518 (86.0%)	
Pseudoexfoliative glaucoma	114 (12.2%)	84 (4.8%)	
PACG	84 (9.0%)	46 (2.6%)	
Pigmentary glaucoma	22 (2.4%)	25 (1.4%)	
Uveitic	21 (2.2%)	60 (3.4%)	
PCG	1 (0.1%)	7 (0.4%)	
Other secondary glaucoma	50 (5.4%)	21 (1.2%)	
Unknown	0 (0%)	4 (0.2%)	
Lens status, no eyes (%)			**<0.001**
Phakic	417 (44.7%)	1519 (86.1%)	
PCIOL	506 (54.2%)	244 (13.8%)	
ACIOL	6 (0.6%)	0 (0%)	
Aphakic	4 (0.4%)	2 (0.1%)	
Unknown	1 (0.1%)	0 (0%)	
Previous LTP, no eyes (%)	296 (31.7%)	44 (2.5%)	**<0.001**
Previous glaucoma surgery, no eyes (%)	209 (22.4%)	129 (7.3%)	**<0.001**
Previous VR Surgery, no eyes (%)	45 (4.8%)	32 (1.8%)	**<0.001**
Previous corneal transplantation	27 (2.9%)	3 (0.2%)	0.18
Surgery performed, no eyes (%)			**<0.001**
Stand-alone	825 (88.3%)	1075 (60.9%)	
Combined with CEIOL	105 (11.3%)	689 (39.0%)	

Combined with Express removal	2 (0.2%)	0 (0%)	
Combined with Xen removal	1 (0.1%)	0 (0%)	
Combined with anterior vitrectomy	1 (0.1%)	0 (0%)	
Combined with ACIOL	0 (0%)	1 (0.1%)	

ACIOL: anterior chamber intraocular lens; BCVA: best-corrected visual acuity; CCT: central corneal thickness; CEIOL: cataract extraction and intraocular lens implantation; DS: deep sclerectomy; IQR: interquartile range; IOP: intraocular pressure; LTP: laser trabeculoplasty; MD: mean deviation; NTG: normal-tension glaucoma; OHT: ocular hypertension; PACG: primary angle-closure glaucoma; PCG: primary congenital glaucoma; PCIOL: posterior chamber intraocular lens; POAG: primary open-angle glaucoma; SD: Standard deviation; VR: vitreoretinal.

Table 3. Five-year incidence of hypotony calculated using some selected hypotony criteria.

	Trabeculectomy	**Deep Sclerectomy**
Trabeculectomy	Estimate (95% CI)	Estimate (95% CI)
IOP<5 mmHg (any visit)	49.6% (45.8-53.1%)	43.0% (40.2-45.6%)
IOP<6 mmHg (any visit)	60.3% (56.4-63.8%)	51.2% (48.4-53.8%)
IOP<6 mmHg (2 consecutive visits after >3 months from surgery)	21.9% (18.5-25.3%)	8.5% (6.8-10.2%)
Hypotony Maculopathy	3.5% (2.1-4.9%)	3.0% (1.9-4.0%)
Hypotony complications	13.0% (10.7-15.3%)	7.3% (5.0.8-8.7%)
Revision for hypotony	4.9% (3.3-6.5%)	2.3% (1.3-3.4%)

CI: confidence interval; IOP: intraocular pressure.

Table 4. Sensitivity and specificity of the various numerical criteria to identify clinical complications

	Trabeculectomy		**Deep sclerectomy**	
Hypotony criteria	Sensitivity	Specificity	Sensitivity	Specificity
IOP<4mmHg (any visit)	68.9%	74.2%	77.3%	72.7%
IOP<4 mmHg (any visit after >2 months)	32.8%	86.9%	39.5%	93.0%
IOP<4 mmHg (last visit)	5.9%	97.1%	2.5%	98.6%
IOP<4mmHg (2 consecutive visits)	43.7%	89.6%	27.7%	95.9%
IOP<5 mmHg (any visit)	87.4%	58.9%	88.2%	62.1%
IOP<5 mmHg (any visit after >4 weeks)	52.9%	72.0%	48.7%	87.7%
IOP<5mmHg (any visit after >3 months)	43.7%	77.3%	42.0%	90.0%
IOP<5mmHg (any visit after ≥6 months)	36.1%	79.9%	36.1%	91.3%
IOP<5mmHg (2 consecutive visits)	56.3%	79.5%	42.9%	91.1%
IOP<5mmHg (2 consecutive visits after >1 month)	31.1%	85.5%	25.2%	95.3%
IOP<5mmHg (2 consecutive visits after >3 months)	10.9%	96.7%	21.0%	96.4%
IOP<5mmHg (2 consecutive visits after >3 months or last visit)	17.6%	91.4%	22.7%	95.2%
IOP<5mmHg (last visit)	12.6%	93.1%	4.2%	97.8%
IOP<6 mmHg (any visit)	96.6%	49.4%	95.8%	53.6%
IOP<6mmHg (any visit after >1 month)	65.5%	63.3%	55.5%	82.3%
IOP<6mmHg (2 consecutive visits)	66.4%	71.0%	52.9%	85.6%
IOP<6mmHg (2 consecutive visits after >1 week)	57.1%	73.0%	50.4%	86.0%
IOP<6mmHg (2 consecutive visits after >1 month)	42.0%	79.4%	35.3%	91.6%
IOP<6mmHg (2 consecutive visits after >6 weeks)	38.7%	81.2%	31.9%	92.5%
IOP<6 mmHg (2 consecutive visits after >3 months)	31.9%	84.2%	30.3%	94.0%
IOP<6mmHg after >3 months and confirmed >1 month later	21.0%	86.4%	24.4%	95.5%
IOP<6mmHg (2 consecutive visits >6 months)	25.2%	86.1%	26.9%	95.0%
IOP<6mmHg (for >2 months)	25.2%	86.0%	25.2%	94.8%
IOP<6mmHg (2 consecutive visits for ≥2 months after >1 week)	25.2%	86.1%	24.4%	95.0%
IOP<6mmHg (2 consecutive visits ≥3 weeks apart)	32.8%	81.7%	33.6%	92.0%
IOP<6mmHg for >6 months	15.1%	91.9%	18.5%	96.5%
IOP<6mmHg (last visit)	16.0%	89.8%	8.4%	96.2%
IOP<8mmHg (last visit)	25.2%	77.9%	16.0%	90.3%
IOP<10mmHg (any visit)	100%	11.9%	98.3%	26.1%

CI: confidence interval; IOP: intraocular pressure.

Table 9. Five-year success rates calculated using some selected hypotony criteria.				
	Criteria A	**Criteria B**	**Criteria C**	**Criteria D**
Trabeculectomy	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
IOP<5 mmHg (any visit)	19.5% (16.6-22.9%)	17.8% (15-21.2%)	13.1% (10.6-16.2%)	8.5% (6.5-11.2%)
IOP<6 mmHg (any visit)	13.2% (10.7-16.2%)	11.7% (9.3-14.7%)	8.0% (6.0-10.7%)	5.3% (3.7-7.6%)
IOP<6 mmHg (2 consecutive visits after >3 months from surgery)	29.1% (25.6-33.1%)	27.3% (23.8-31.2%)	19.8% (16.7-23.6%)	13.3% (10.6-16.7%)
Hypotony Maculopathy	39.3% (35.5-43.5%)	37.4% (33.6-41.6%)	29.6% (25.9-33.8%)	21.9% (18.7-25.8%)
Hypotony complications	35.5% (31.8-39.6%)	33.8% (30.1-38.0%)	26.9% (23.4-31.0%)	20.5% (17.3-24.2%)
Revision for hypotony	38.8% (35.0-43.0%)	36.7% (33.0-40.9%)	29.1% (25.4-33.2%)	22.1% (18.8-25.9%)
Deep Sclerectomy				
IOP<5 mmHg (any visit)	35.0% (32.4-37.9%)	31.0% (28.4-33.8%)	17.8% (15.6-20.2%)	5.7% (4.3-7.5%)
IOP<6 mmHg (any visit)	29.7% (27.2-32.4%)	26.2% (23.8-28.9%)	14.4% (12.5-16.7%)	4.2% (3-5.9%)
IOP<6 mmHg (2 consecutive visits after >3 months from surgery)	56.2% (53.3-59.3%)	51.0% (48.0-54.1%)	32.7% (30,0-35.7%)	11.7% (9.9-13.9%)
Hypotony Maculopathy	60.4% (57.5-63.4%)	54.9% (52.0-58.0%)	35.9% (33.2-38.9%)	13.8% (11.8-16.2%)
Hypotony complications	57.8% (55-60.8%)	52.6% (49.7-55.6%)	34.3% (31.5-37.3%)	13.1% (11.1-15.4%)
Revision for hypotony	60.7% (57.9-63.7%)	55.2% (52.3-58.3%)	36.1% (33.3-39.1%)	14.4% (12.3-16.7%)
CI: confidence interval; IOP: intraocular pressure.				

Supplemental Figure S2

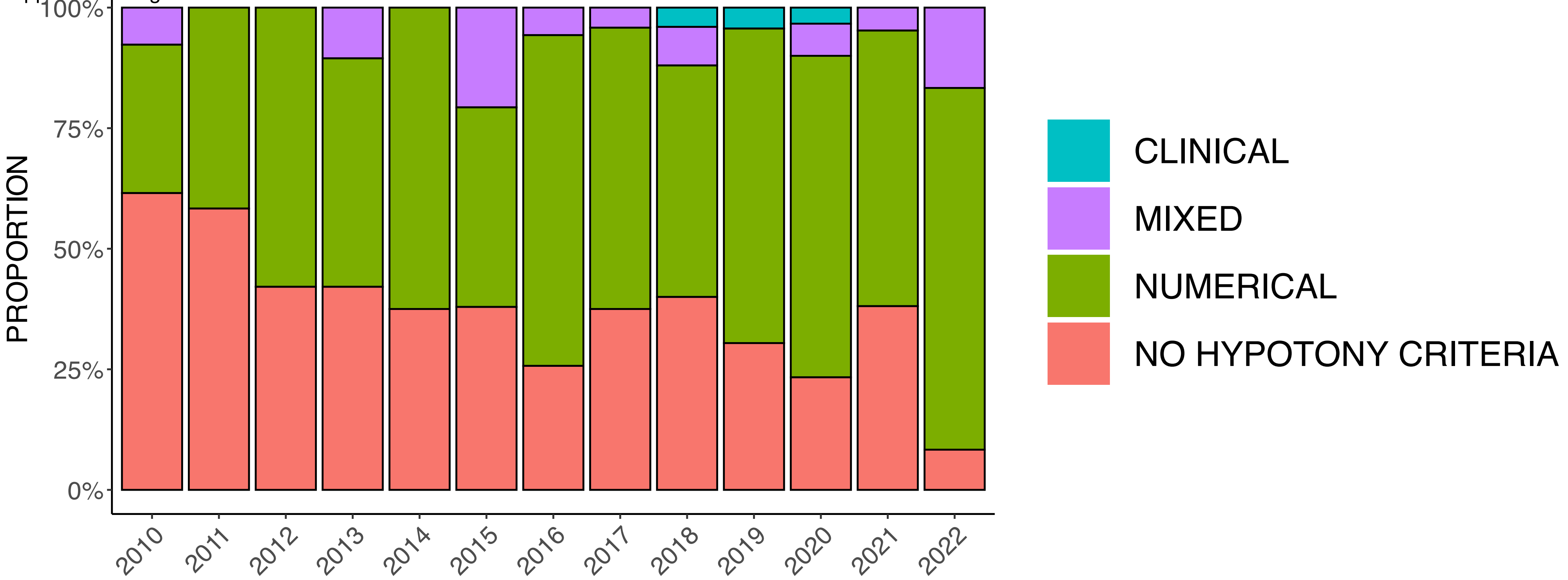

Figure S2. Proportion of types of hypotony used as failure criteria in the included studies over time.

Supplemental Figure S3

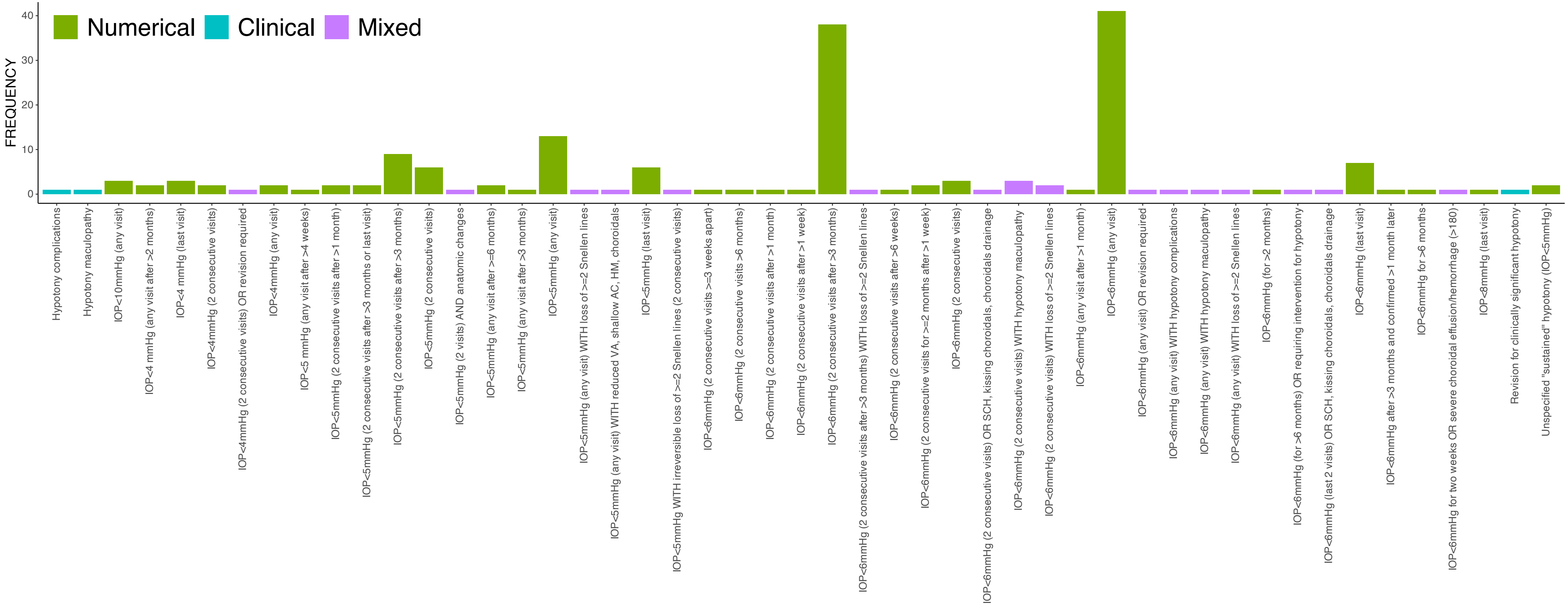

Figure S3. Bar plot illustrating the frequency of individual hypotony definitions used as failure criteria in the included studies. AC: anterior chamber; HM: hypotony maculopathy; IOP: intraocular pressure; SCH: suprachoroidal hemorrhage; VA: visual acuity.

Supplemental Figure S6

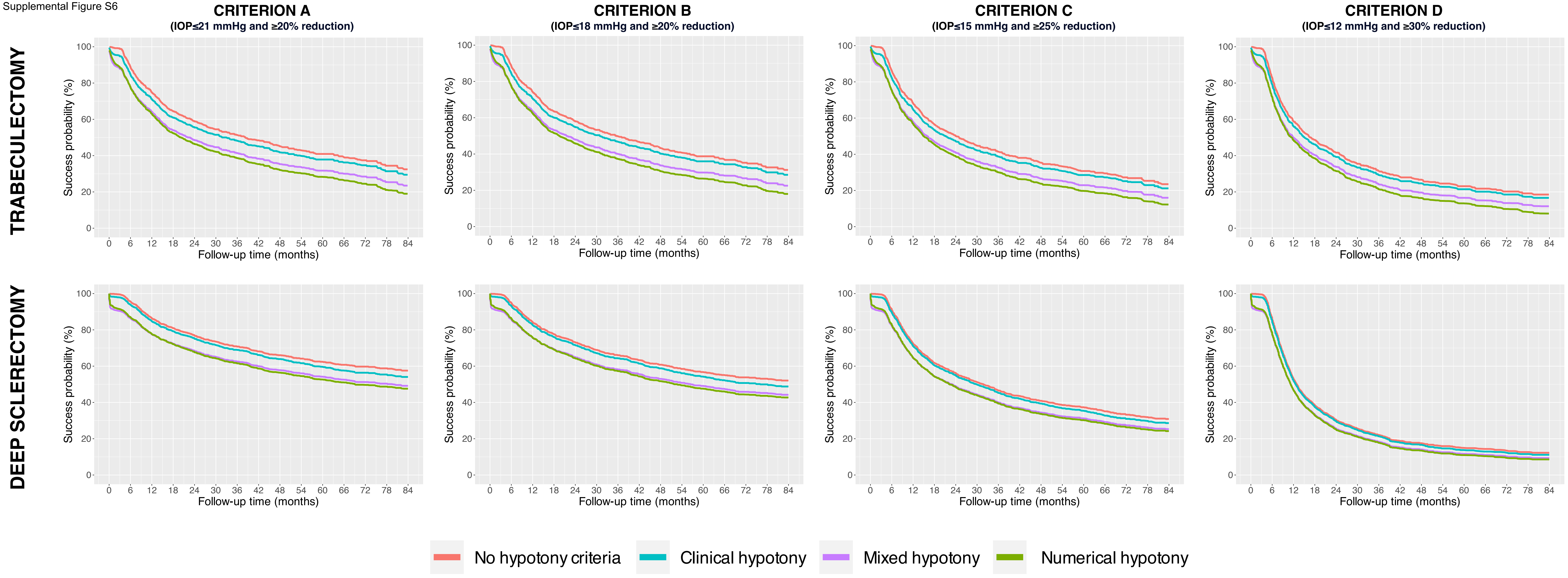

Figure S6. Kaplan-Meier success rates for different composite criteria categorized by the type of hypotony (clinical, mixed, and numerical) as a failure criterion in the trabeculectomy (top row) and deep sclerectomy (bottom row) groups.

Supplemental Figure S7

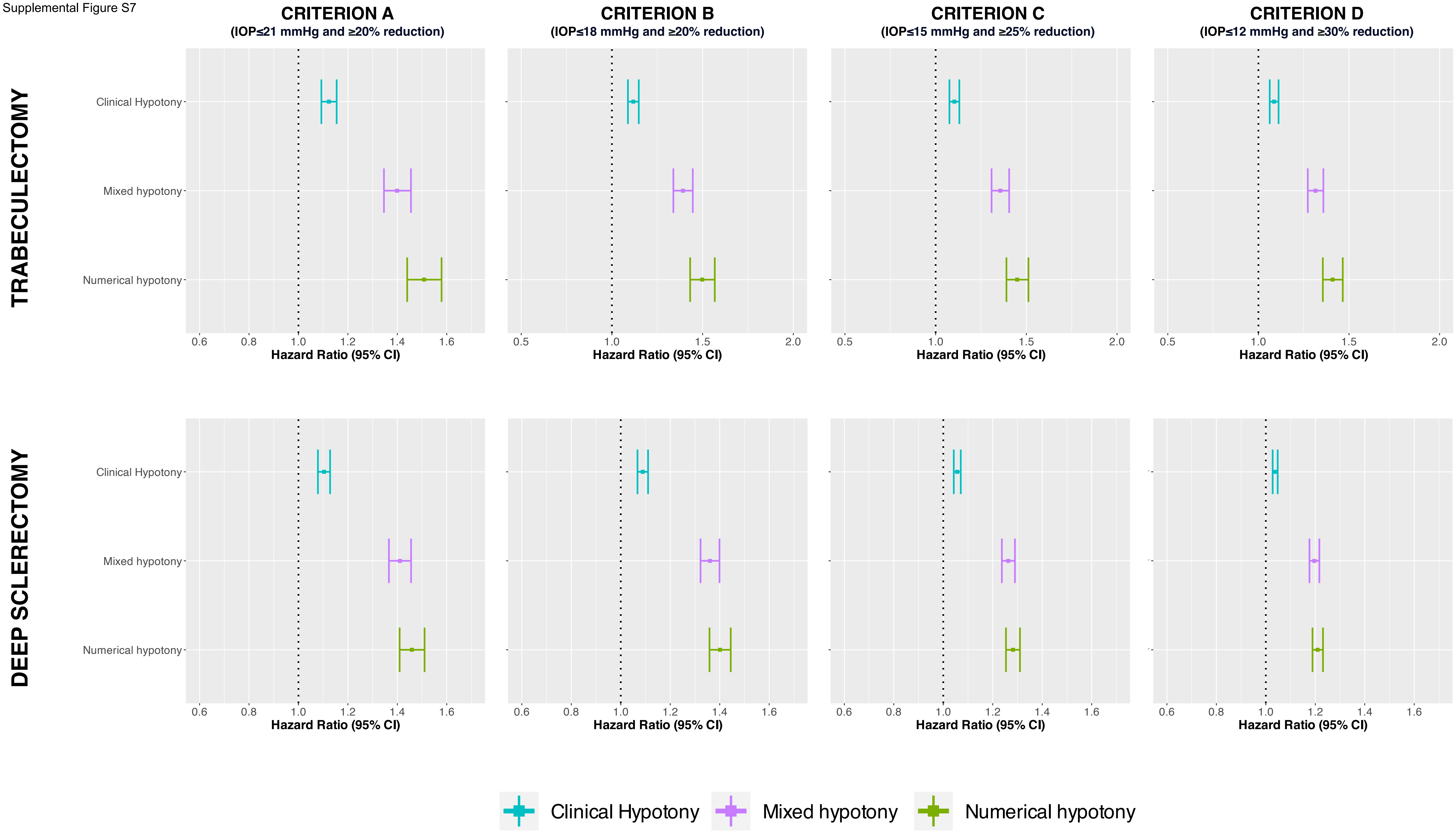

Figure S7. Forest plot displaying the risk of failure for various composite criteria, differentiated by the type of hypotony (clinical, mixed, and numerical) used as a failure criterion, in comparison to having no hypotony failure criteria. Dots and bars represent hazard ratios (HRs) and 95% confidence intervals (95% CIs).

Supplemental Figure S8

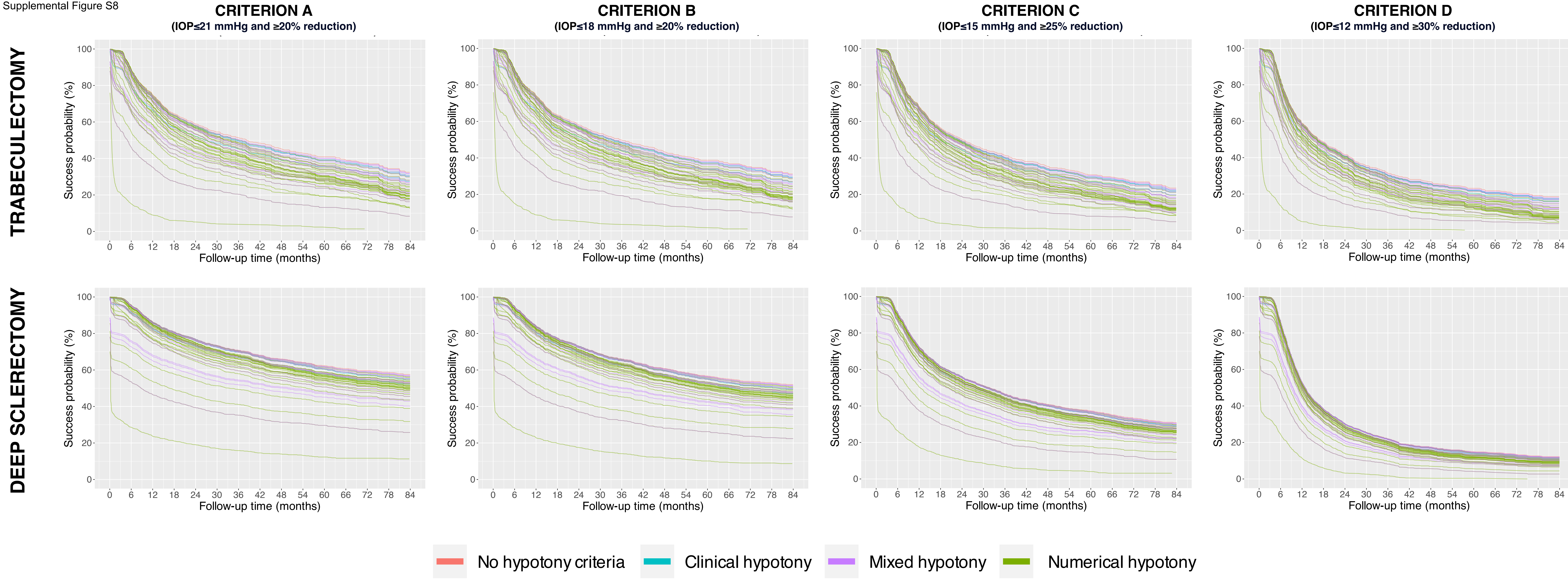

Figure S8. Kaplan-Meier success rates for the various composite criteria stratified as a function of the individual hypotony failure criterion in the trabeculectomy (top row) and deep sclerectomy (bottom row) arm.

Supplemental Figure S9

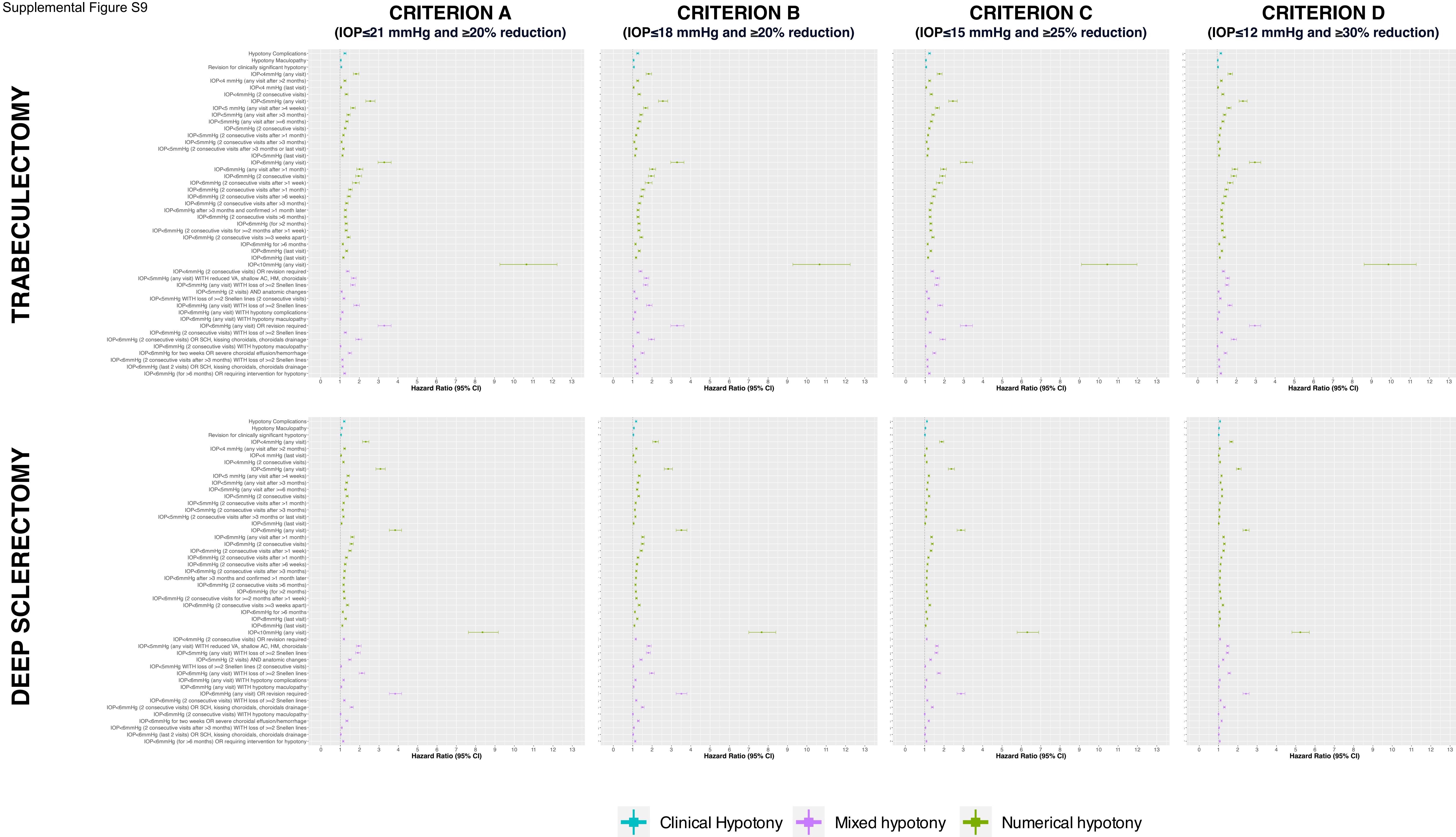

Figure S9. Forest plot illustrating the risk of failure for various composite criteria, categorized by the individual hypotony criterion used to define failure. Dots and bars represent hazard ratios (HRs) and 95% confidence intervals (95% CIs). AC: anterior chamber; HM: hypotony maculopathy; IOP: intraocular pressure; SCH: suprachoroidal hemorrhage; VA: visual acuity.

Table S2. Five-year incidence of hypotony calculated using the various literature-based hypotony failure criteria in the trabeculectomy cohort

	Trabeculectomy	**Deep sclerectomy**
Hypotony criteria	Estimate (95% CI)	Estimate (95% CI)
Hypotony complications	13.0% (10.7-15.3%)	7.3% (5.0.8-8.7%)
Hypotony Maculopathy	3.5% (2.1-4.9%)	3.0% (1.9-4.0%)
Revision for hypotony	4.9% (3.3-6.5%)	2.3% (1.3-3.4%)
IOP<4mmHg (any visit)	33.4% (29.8-36.8%)	31.7% (29.2-34.1%)
IOP<4 mmHg (any visit after >2 months)	18.7% (15.4-21.9%)	10.6% (8.7-12.3%)
IOP<4 mmHg (last visit)	3.3% (1.8-4.8%)	0.8% (0.3-1.4%)
IOP<4mmHg (2 consecutive visits)	16.4% (13.6-19%)	6.0% (4.8-7.3%)
IOP<5 mmHg (any visit)	49.6% (45.8-53.1%)	43.0% (40.2-45.6%)
IOP<5 mmHg (any visit after >4 weeks)	35.7% (31.8-39.3%)	16.6% (14.4-18.8%)
IOP<5mmHg (any visit after >3 months)	29.9% (26.2-33.5%)	14.2% (12.1-16.3%)
IOP<5mmHg (any visit after ≥6 months)	27.0% (23.3-30.5%)	12.8% (10.7-14.8%)
IOP<5mmHg (2 consecutive visits)	27.5% (24.1-30.8%)	11.4% (9.7-13.1%)
IOP<5mmHg (2 consecutive visits after >1 month)	19.0% (15.8-22.1%)	6.6% (5.1-8.0%)
IOP<5mmHg (2 consecutive visits after >3 months)	5.5% (3.5-7.5%)	5.3% (3.9-6.7%)
IOP<5mmHg (2 consecutive visits after >3 months or last visit)	11.4%	6.2%

	(8.7-14.0%)	(4.7-7.7%)
IOP<5mmHg (last visit)	7.8% (5.5-10.0%)	1.6% (0.8-2.5%)
IOP<6 mmHg (any visit)	60.3% (56.4-63.8%)	51.2% (48.4-53.8%)
IOP<6mmHg (any visit after >1 month)	47.5% (43.4-51.3%)	22.9% (20.4-25.3%)
IOP<6mmHg (2 consecutive visits)	36.9% (33.2-40.4%)	18.0% (15.9-20.1%)
IOP<6mmHg (2 consecutive visits after >1 week)	34.2% (30.5-37.7%)	17.6% (15.4-19.6%)
IOP<6mmHg (2 consecutive visits after >1 month)	27.2% (23.5-30.7%)	11.1% (9.3-12.9%)
IOP<6mmHg (2 consecutive visits after >6 weeks)	25.0% (21.4-28.5%)	10.1% (8.3-11.8%)
IOP<6 mmHg (2 consecutive visits after >3 months)	21.9% (18.5-25.3%)	8.5% (6.8-10.2%)
IOP<6mmHg after >3 months and confirmed >1 month later	17.7% (14.4-20.9%)	6.2% (4.7-7.6%)
IOP<6mmHg (2 consecutive visits >6 months)	19.7% (16.4-23%)	7.3% (5.7-8.9%)
IOP<6mmHg (for >2 months)	18.3% (15.0-21.5%)	6.7% (5.1-8.2%)
IOP<6mmHg (2 consecutive visits for ≥2 months after >1 week)	18.2% (14.9-21.4%)	6.4% (4.9-7.8%)
IOP<6mmHg (2 consecutive visits ≥3 weeks apart)	23.0% (19.5-26.3%)	10.1% (8.3-11.9%)
IOP<6mmHg for >6 months	11.5% (8.7-14.3%)	3.9% (2.7-5.1%)
IOP<6mmHg (last visit)	10.8% (8.3-13.3%)	2.7% (1.6-3.7%)
IOP<8mmHg (last visit)	20.0% (16.7-23.2%)	8.4% (6.6-10.2%)
IOP<10mmHg (any visit)	92.0%	78.4%

	(89.7-93.8%)	(76.0-80.6%)
IOP<4mmHg (2 consecutive visits) OR revision required	18.3% (15.4-21.1%)	7.5% (6.0-9.0%)
IOP<5mmHg (any visit) WITH reduced VA, shallow AC, HM, choroidals	30.8% (27.3-34.1%)	23.8% (21.5-26.0%)
IOP<5mmHg (any visit) WITH loss of ≥2 Snellen lines	29.5% (26.1-32.8%)	23.0% (20.8-25.2%)
IOP<5mmHg (2 visits) AND anatomic changes	4.7% (3.2-6.1%)	1.1% (0.4-1.7%)
IOP<5mmHg WITH loss of ≥2 Snellen lines (2 consecutive visits)	12.5% (9.9-15%)	4.8% (3.7-5.9%)
IOP<6mmHg (any visit) WITH loss of ≥2 Snellen lines	36.3% (32.5-39.8%)	27.0% (24.7-29.3%)
IOP<6mmHg (any visit) WITH hypotony complications	6.9% (5.1-8.7%)	6.0% (4.7-7.3%)
IOP<6mmHg (any visit) WITH hypotony maculopathy	1.9% (0.8-3.0%)	2.5% (1.5-3.4%)
IOP<6mmHg (any visit) OR revision required	60.4% (56.5-63.9%)	51.2% (48.4-53.7%)
IOP<6mmHg (2 consecutive visits) WITH loss of ≥2 Snellen lines	15.4% (12.6-18.1%)	9.1% (7.5-10.6%)
IOP<6mmHg (2 consecutive visits) OR SCH, kissing choroidals, choroidals drainage	37.3% (33.6-40.9%)	18.3% (16.2-20.4%)
IOP<6mmHg (2 consecutive visits) WITH hypotony maculopathy	0.8% (0.2-1.5%)	1.4% (0.7-2.1%)
IOP<6mmHg for two weeks OR severe choroidal effusion/hemorrhage	26.2% (22.6-29.6%)	11.1% (9.3-12.9%)
IOP<6mmHg (2 consecutive visits after >3 months) WITH loss of ≥2 Snellen lines	10.4% (7.9-12.9%)	3.8% (2.6-4.9%)
IOP<6mmHg (last 2 visits) OR SCH, kissing choroidals, choroidals drainage	7.3% (5.1-9.5%)	0.9% (0.4-1.3%)
IOP<6mmHg for >6 months OR requiring intervention for hypotony	15.0% (11.9-18.0%)	5.2% (3.8-6.6%)

AC: anterior chamber; CI: confidence interval; IOP: intraocular pressure; HM: hypotony maculopathy; SCH: suprachoroidal hemorrhage

Table S5. Five-year success rates calculated using different types of hypotony criteria.				
	Criteria A	**Criteria B**	**Criteria C**	**Criteria D**
Trabeculectomy	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
No hypotony criteria	40.9% (37.1-45.1%)	38.7% (34.9-42.9%)	30.7% (27.0-35.0%)	23.2% (19.9-27.0%)
Clinical hypotony	37.9% (34.2-41.9%)	36.0% (32.3-40.1%)	28.5% (25.0-32.6%)	21.5% (18.3-25.2%)
Mixed hypotony	31.7% (28.6-35.3%)	29.8% (26.6-33.3%)	22.9% (20.0-26.3%)	16.7% (14.2-19.8%)
Numerical hypotony	28.3% (25.4-31.6%)	26.5% (23.6-29.7%)	19.8% (17.1-22.9%)	13.7% (11.4-16.4%)
Deep Sclerectomy				
No hypotony criteria	62.4% (59.6-65.3%)	56.8% (53.9-59.8%)	37.4% (34.6-40.4%)	15.0% (12.9-17.4%)
Clinical Hypotony	59.7% (56.8-62.6%)	54.3% (51.4-57.3%)	35.4% (32.7-38.4%)	13.8% (11.8-16.0%)
Mixed hypotony	54.2% (51.6-56.9%)	49.1% (46.5-51.9%)	31.2% (28.8-33.9%)	11.7% (10.0-13.6%)
Numerical hypotony	52.6% (50.1-55.3%)	47.6% (45.0-50.3%)	30.2% (27.9-32.9%	11.0% (9.3-12.9%)
CI: confidence interval; HR: hazard ratio.				

Table S6. Cox Regression Models for the risk of failure using different types of hypotony criteria.

	Criteria A Failure		**Criteria B Failure**		**Criteria C Failure**		**Criteria D Failure**	
Hypotony type (ref: no hypotony criteria)	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Trabeculectomy								
Clinical hypotony	1.12 (1.09-1.15)	**<0.001**	1.12 (1.09-1.15)	**<0.001**	1.10 (1.08-1.13)	**<0.001**	1.09 (1.06-1.11)	**<0.001**
Mixed hypotony	1.40 (1.35-1.46)	**<0.001**	1.39 (1.34-1.45)	**<0.001**	1.36 (1.31-1.41)	**<0.001**	1.31 (1.27-1.36)	**<0.001**
Numerical hypotony	1.51 (1.44-1.58)	**<0.001**	1.50 (1.43-1.57)	**<0.001**	1.45 (1.39-1.51)	**<0.001**	1.41 (1.36-1.47)	**<0.001**
Deep Sclerectomy								
Clinical Hypotony	1.10 (1.08-1.13)	**<0.001**	1.09 (1.07-1.11)	**<0.001**	1.06 (1.04-1.07)	**<0.001**	1.04 (1.03-1.05)	**<0.001**
Mixed hypotony	1.41 (1.37-1.46)	**<0.001**	1.36 (1.32-1.4)	**<0.001**	1.26 (1.24-1.29)	**<0.001**	1.20 (1.18-1.22)	**<0.001**
Numerical hypotony	1.46 (1.41-1.51)	**<0.001**	1.40 (1.36-1.44)	**<0.001**	1.28 (1.25-1.31)	**<0.001**	1.21 (1.19-1.23)	**<0.001**

CI: confidence interval; HR: hazard ratio.

Table S7. Five-year success rates calculated using the various literature-based hypotony failure criteria in the trabeculectomy cohort

	Criteria A	**Criteria B**	**Criteria C**	**Criteria D**
Trabeculectomy	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
No hypotony criteria	40.9% (37.1-45.1%)	38.7% (34.9-42.9%)	30.7% (27.0-35.0%)	23.2% (19.9-27.0%)
Hypotony complications	35.5% (31.8-39.6%)	33.8% (30.1-38.0%)	26.9% (23.4-31.0%)	20.5% (17.3-24.2%)
Hypotony Maculopathy	39.3% (35.5-43.5%)	37.4% (33.6-41.6%)	29.6% (25.9-33.8%)	21.9% (18.7-25.8%)
Revision for hypotony	38.8% (35.0-43.0%)	36.7% (33.0-40.9%)	29.1% (25.4-33.2%)	22.1% (18.8-25.9%)
IOP<4mmHg (any visit)	26.4% (23.1-30.2%)	24.7% (21.4-28.5%)	18.7% (15.6-22.3%)	13.5% (10.9-16.8%)
IOP<4 mmHg (any visit after >2 months)	32.1% (28.5-36.2%)	30.2% (26.6-34.3%)	22.7% (19.3-26.6%)	16.3% (13.4-19.9%)
IOP<4 mmHg (last visit)	39.0% (35.2-43.2%)	36.8% (33.1-41.0%)	29.0% (25.3-33.1%)	21.5% (18.3-25.3%)
IOP<4mmHg (2 consecutive visits)	33.0% (29.4-37.0%)	30.9% (27.4-34.9%)	23.2% (19.8-27.1%)	17.1% (14.2-20.5%)
IOP<5 mmHg (any visit)	19.5% (16.6-22.9%)	17.8% (15.0-21.2%)	13.1% (10.6-16.2%)	8.5% (6.5-11.2%)
IOP<5 mmHg (any visit after >4 weeks)	26.1% (22.8-29.8%)	25.6% (22.2-29.5%)	17.8% (14.8-21.3%)	11.7% (9.2-14.8%)
IOP<5mmHg (any visit after >3 months)	27.4% (24.0-31.3%)	25.6% (22.2-29.5%)	18.95 (15.8-22.55)	12.6% (10.0-15.8%)
IOP<5mmHg (any visit after ≥6 months)	28.0% (24.5-32.0%)	26.1% (22.7-30.0%)	19.1% (16.0-22.8%)	12.8% (10.2-16.1%)
IOP<5mmHg (2 consecutive visits)	30.3% (26.8-34.2%)	28.5% (25.1-32.4%)	22.5% (19.3-26.2%)	16.1% (13.4-19.4%)
IOP<5mmHg (2 consecutive visits after >1 month)	34.0% (30.3-38.0%)	32.1% (28.5-36.1%)	24.7% (21.3-28.6%)	17.8% (14.9-21.2%)
IOP<5mmHg (2 consecutive visits after >3 months)	37.2% (33.4-41.3%)	35.1% (31.4-39.3%)	27.2% (23.7-31.4%)	19.9% (16.7-23.6%)

IOP<5mmHg (2 consecutive visits after >3 months or last visit)	33.9% (30.3-37.8%)	31.9% (28.4-35.9%)	24.3% (21.0-28.2%)	17.2% (14.3-20.6%)
IOP<5mmHg (last visit)	36.2% (32.6-40.3%)	34.2% (30.6-38.2%)	26.5% (23.1-30.5%)	19.2% (16.2-22.7%)
IOP<6 mmHg (any visit)	13.2% (10.7-16.2%)	11.7% (9.3-14.7%)	8.0% (6.0-10.7%)	5.3% (3.7-7.6%)
IOP<6mmHg (any visit after >1 month)	19.3% (16.4-22.8%)	17.9% (15-21.4%)	12.5% (10-15.7%)	7.5% (5.6-10.2%)
IOP<6mmHg (2 consecutive visits)	23.7% (20.5-27.4%)	21.9% (18.8-25.6%)	16.1% (13.3-19.5%)	10.1% (7.8-13.0%)
IOP<6mmHg (2 consecutive visits after >1 week)	24.6% (21.2-28.5%)	23.0% (19.7-26.9%)	15.9% (13.0-19.5%)	10.0% (7.7-13.1%)
IOP<6mmHg (2 consecutive visits after >1 month)	28.0% (24.5-31.9%)	26.1% (22.6-30.0%)	18.8% (15.8-22.5%)	12.4% (9.8-15.6%)
IOP<6mmHg (2 consecutive visits after >6 weeks)	28.3% (24.9-32.3%)	26.4% (23.0-30.3%)	19.2% (16.1-22.9%)	12.9% (10.3-16.2%)
IOP<6 mmHg (2 consecutive visits after >3 months)	29.1% (25.6-33.1%)	27.3% (23.8-31.2%)	19.8% (16.7-23.6%)	13.3% (10.6-16.7%)
IOP<6mmHg after >3 months and confirmed >1 month later	30.7% (27.1-34.7%)	28.5% (25.0-32.5%)	21.0% (17.8-24.8%)	14.3% (11.6-17.7%)
IOP<6mmHg (2 consecutive visits >6 months)	29.7% (26.1-33.7%)	27.8% (24.3-31.8%)	26.1% (22.6-30.1%)	13.6% (10.8-17.0%)
IOP<6mmHg (for >2 months)	30.3% (26.8-34.3%)	28.2% (24.7-32.1%)	20.8% (17.6-24.5%)	14.3% (11.6-17.7%)
IOP<6mmHg (2 consecutive visits for ≥2 months after >1 week)	30.2% (26.7-34.3%)	28.1% (24.6-32.1%)	20.7% (17.6-24.5%)	10.0% (7.7-13.1%)
IOP<6mmHg (2 consecutive visits ≥3 weeks apart)	28.7% (25.3-32.7%)	26.8% (23.4-30.7%)	20.0% (16.9-23.6%)	13.5% (10.9-16.8%)
IOP<6mmHg for >6 months	35.9% (32.2-40.0%)	33.8% (30.1-37.9%)	26.1% (22.6-30.1%)	18.6% (15.7-22.2%)
IOP<6mmHg (last visit)	34.9% (31.3-38.9%)	32.8% (29.3-36.8%)	25.3% (21.9-29.2%)	18.1% (15.2-21.5%)
IOP<8mmHg (last visit)	30.0% (26.7-33.8%)	28.2% (24.9-31.9%)	21.4% (18.4-25.0%)	15.0% (12.4-18%)

IOP<10mmHg (any visit)	2.4% (1.5-4.0%)	1.9% (1.1-3.4%)	0.7% (0.3-2.0%)	0.2% (0.0-1.3%)
IOP<4mmHg (2 consecutive visits) OR revision required	30.9% (27.4-34.9%)	29.0% (25.5-32.9%)	21.6% (18.4-25.4%)	16.3% (13.5-19.7%)
IOP<5mmHg (any visit) WITH reduced VA, shallow AC, HM, choroidals	28.3% (24.9-32.2%)	26.6% (23.2-30.6%)	20.5% (17.3-24.2%)	15.2% (12.4-18.6%)
IOP<5mmHg (any visit) WITH loss of ≥2 Snellen lines	28.9% (25.4-32.8%)	27.0% (23.6-30.9%)	20.8% (17.6-24.6%)	15.4% (12.6-18.8%)
IOP<5mmHg (2 visits) AND anatomic changes	38.8% (35.1-43.0%)	36.7% (33.0-40.9%)	29.2% (25.5-33.3%)	21.7% (18.5-25.5%)
IOP<5mmHg WITH loss of ≥2 Snellen lines (2 consecutive visits)	35.7% (32.0-39.8%)	33.6% (29.9-37.7%)	26.5% (23.0-30.5%)	19.5% (16.3-23.2%)
IOP<6mmHg (any visit) WITH loss of ≥2 Snellen lines	24.8% (21.5-28.7%)	23.2% (19.9-27.0%)	17.1% (14.1-20.8%)	12.9% (10.2-16.2%)
IOP<6mmHg (any visit) WITH hypotony complications	38.1% (34.3-42.2%)	36.1% (32.4-40.3%)	28.6% (25-32.7%)	21.6% (18.4-25.4%)
IOP<6mmHg (any visit) WITH hypotony maculopathy	39.8% (36.0-44.0%)	37.7% (33.9-41.9%)	30.0% (26.3-34.2%)	22.4% (19.1-26.2%)
IOP<6mmHg (any visit) OR revision required	13.2% (10.7-16.2%)	11.7% (9.3-14.7%)	8.0% (6.0-10.7%)	5.3% (3.7-7.6%)
IOP<6mmHg (2 consecutive visits) WITH loss of ≥2 Snellen lines	34.2% (30.6-38.3%)	32.2% (28.5-36.2%)	25.0% (21.6-29.0%)	18.5% (15.4-22.2%)
IOP<6mmHg (2 consecutive visits) OR SCH, kissing choroidals, choroidals drainage	23.7% (20.5-27.4%)	21.9% (18.8-25.6%)	16.1% (13.2-19.5%)	10.1% (7.8-13.1%)
IOP<6mmHg (2 consecutive visits) WITH hypotony maculopathy	40.2% (36.4-44.4%)	38.0% (34.2-42.2%)	30.3% (26.6-34.4%)	22.5% (19.3-26.3%)
IOP<6mmHg for two weeks OR severe choroidal effusion/hemorrhage	27.8% (24.4-31.7%)	25.9% (22.5-29.7%)	19.1% (16.1-22.7%)	10.1% (7.8-13.1%)
IOP<6mmHg (2 consecutive visits after >3 months) WITH loss of ≥2 Snellen lines	35.6% (31.9-39.8%)	33.6% (29.9-37.8%)	25.9% (22.4-30.0%)	19.2% (16-22.9%)
IOP<6mmHg (last 2 visits) OR SCH, kissing choroidals, choroidals drainage	36.3% (32.7-40.4%)	34.2% (30.6-38.3%)	26.5% (23.1-30.5%)	19.4% (16.3-23.0%)
IOP<6mmHg for >6 months OR requiring intervention for hypotony	31.8% (28.1-35.9%)	29.7% (26.1-33.8%)	22.1% (18.8-26.0%)	15.7% (12.8-19.1%)

AC: anterior chamber; CI: confidence interval; IOP: intraocular pressure; HM: hypotony maculopathy; SCH: suprachoroidal hemorrhage

Table S8. Five-year success rates calculated using the various literature-based hypotony failure criteria in the deep sclerectomy cohort				
	Criteria A	**Criteria B**	**Criteria C**	**Criteria D**
Deep Sclerectomy	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
No hypotony criteria	62.4% (59.6-65.3%)	56.8% (53.9-59.8%)	37.4% (34.6-40.4%)	15.0% (12.9-17.4%)
Hypotony complications	57.8% (55.0-60.8%)	52.6% (49.7-55.6%)	34.3% (31.5-37.3%)	13.1% (11.1-15.4%)
Hypotony Maculopathy	60.4% (57.5-63.4%)	54.9% (52.0-58.0%)	35.9% (33.2-38.9%)	13.8% (11.8-16.2%)
Revision for hypotony	60.7% (57.9-63.7%)	55.2% (52.3-58.3%)	36.1% (33.3-39.1%)	14.4% (12.3-16.7%)
IOP<4mmHg (any visit)	42.3% (39.6-45.3%)	37.6% (34.8-40.5%)	22.7% (20.4-25.4%)	8.3% (6.7-10.3%)
IOP<4 mmHg (any visit after >2 months)	56.5% (53.6-59.6%)	51.3% (48.4-54.4%)	33.2% (30.5-36.2%)	13.0% (11.0-15.3%)
IOP<4 mmHg (last visit)	61.8% (59.0-64.7%)	56.2% (53.3-59.2%)	36.9% (34.1-39.9%)	14.6% (12.6-16.9%)
IOP<4mmHg (2 consecutive visits)	58.9% (56.1-61.8%)	53.4% (50.6-56.5%)	34.4% (31.6-37.3%)	13.3% (11.4-15.6%)
IOP<5 mmHg (any visit)	35.0% (32.4-37.9%)	31.0% (28.4-33.8%)	17.8% (15.6-20.2%)	5.7% (4.3-7.5%)
IOP<5 mmHg (any visit after >4 weeks)	52.7% (49.8-55.7%)	47.8% (44.9-50.9%)	30.6% (27.9-33.5%)	11.2% (9.4-13.4%)
IOP<5mmHg (any visit after >3 months)	54.0% (51.1-57.1%)	49.1% (46.2-52.2%)	31.6% (28.9-34.6%)	11.9% (10.1-14.1%)
IOP<5mmHg (any visit after ≥6 months)	54.7% (51.8-57.8%)	49.7% (46.7-52.8%)	32.1% (29.3-35.1%)	11.0% (9.1-13.2%)
IOP<5mmHg (2 consecutive visits)	55.4% (52.6-58.4%)	50.2% (47.3-53.2%)	31.6% (28.9-34.5%)	11.7% (9.8-13.9%)
IOP<5mmHg (2 consecutive visits after >1 month)	58.0% (55.1-61.0%)	52.5% (49.6-55.5%)	33.8% (31.1-36.8%)	12.7% (10.8-14.9%)
IOP<5mmHg (2 consecutive visits after >3 months)	58.8% (56.0-61.8%)	53.3% (50.4-56.4%)	34.5% (31.8-37.5%)	13.3% (11.3-15.6%)

IOP<5mmHg (2 consecutive visits after >3 months or last visit)	58.2% (55.4-61.2%)	52.8% (49.9-55.8%)	34.2% (31.5-37.2%)	13.0% (11.1-15.3%)
IOP<5mmHg (last visit)	61.3% (58.5-64.2%)	55.7% (52.8-58.7%)	36.6% (33.8-39.6%)	14.3% (12.3-16.7%)
IOP<6 mmHg (any visit)	35.0% (32.4-37.9%)	26.2% (23.8-28.9%)	14.4% (12.5-16.7%)	4.2% (3.0-5.9%)
IOP<6mmHg (any visit after >1 month)	48.4% (45.5-51.4%)	43.9% (41.0-47.0%)	27.6% (25.0-30.4%)	9.1% (7.5-11.1%)
IOP<6mmHg (2 consecutive visits)	50.7% (47.8-53.7%)	45.8% (42.9-48.9%)	27.9% (25.3-30.7%)	9.3% (7.6-11.4%)
IOP<6mmHg (2 consecutive visits after >1 week)	51.9% (49.1-55.0%)	47.0% (44.1-50.1%)	29.2% (26.6-32.1%)	9.7% (8.0-11.8%)
IOP<6mmHg (2 consecutive visits after >1 month)	54.5% (51.6-57.5%)	49.4% (46.5-52.5%)	31.3% (28.6-34.2%)	10.7% (8.9-12.8%)
IOP<6mmHg (2 consecutive visits after >6 weeks)	55.6% (52.7-58.6%)	50.4% (47.5-53.5%)	32.1% (29.4-35.1%)	11.4% (9.6-13.6%)
IOP<6 mmHg (2 consecutive visits after >3 months)	56.2% (53.3-59.3%)	51.0% (48.0-54.1%)	32.7% (30.0-35.7%)	11.7% (9.9-13.9%)
IOP<6mmHg after >3 months and confirmed >1 month later	57.0% (54.1-60.0%)	51.6% (48.7-54.7%)	33.1% (30.4-36.1%)	11.9% (10.0-14.1%)
IOP<6mmHg (2 consecutive visits >6 months)	58.9% (56.0-61.9%)	51.7% (48.8-54.9%)	34.3% (31.6-37.3%)	12.6% (10.7-14.8%)
IOP<6mmHg (for >2 months)	57.5% (54.6-60.5%)	52% (49.1-55.0%)	33.3% (30.6-36.3%)	12.0% (10.2-14.2%)
IOP<6mmHg (2 consecutive visits for ≥2 months after >1 week)	57.0% (54.1-60.0%)	51.4% (48.5-54.5%)	32.8% (30.1-35.7%)	11.6% (9.8-13.8%)
IOP<6mmHg (2 consecutive visits ≥3 weeks apart)	55.3% (52.5-58.3%)	49.9% (47.0-52.9%)	31.5% (28.8-34.4%)	10.8% (9.1-13.0%)
IOP<6mmHg for >6 months	58.9% (56.0-61.9%)	53.3% (50.4-56.3%)	34.3% (31.6-37.3%)	12.6% (10.7-14.8%)
IOP<6mmHg (last visit)	60.5% (57.7-63.4%)	54.9% (52.1-57.9%)	36.0% (33.3-39.0%)	14.1% (12.1-16.4%)
IOP<8mmHg (last visit)	56.4% (53.6-59.3%)	51.0% (48.2-54.0%)	33.1% (30.5-36.0%)	12.2% (10.4-14.4%)

IOP<10mmHg (any visit)	12.3% (10.5-14.4%)	10.1% (8.5-12.2%)	4.1% (3-5.5%)	0.4% (0.1-1.2%)
IOP<4mmHg (2 consecutive visits) OR revision required	57.9% (55.1-60.9%)	52.6% (49.8-55.7%)	33.8% (31.1-36.7%)	13.1% (11.1-15.4%)
IOP<5mmHg (any visit) WITH reduced VA, shallow AC, HM, choroidals	46.9% (44.1-49.9%)	42.2% (39.4-45.2%)	25.9% (23.5-28.7%)	8.9% (7.2-10.9%)
IOP<5mmHg (any visit) WITH loss of ≥2 Snellen lines	47.6% (44.8-50.6%)	42.8% (40.0-45.8%)	26.2% (23.7-29.0%)	9.0% (7.3-11.1%)
IOP<5mmHg (2 visits) AND anatomic changes	53.0% (50.2-56.0%)	48.1% (45.2-51.1%)	30.3% (27.6-33.2%)	10.9% (9.1-13.1%)
IOP<5mmHg WITH loss of ≥2 Snellen lines (2 consecutive visits)	61.5% (58.7-64.4%)	55.9% (53.0-58.9%)	36.6% (33.8-39.6%)	14.6% (12.6-17.0%)
IOP<6mmHg (any visit) WITH loss of ≥2 Snellen lines	45.1% (42.3-48.1%)	40.5% (37.8-43.5%)	24.3% (21.9-27.0%)	8.4% (6.8-10.3%)
IOP<6mmHg (any visit) WITH hypotony complications	58.6% (55.8-61.6%)	53.4% (50.5-56.4%)	34.7% (32.0-37.7%)	13.5% (11.5-15.8%)
IOP<6mmHg (any visit) WITH hypotony maculopathy	60.8% (58.0-63.8%)	55.4% (52.5-58.4%)	36.2% (33.5-39.2%)	14.2% (12.2-16.6%)
IOP<6mmHg (any visit) OR revision required	45.1% (42.3-48.1%)	26.2% (23.8-28.9%)	14.4% (12.5-16.7%)	4.2% (3.0-5.9%)
IOP<6mmHg (2 consecutive visits) WITH loss of ≥2 Snellen lines	58.2% (55.4-61.1%)	52.8% (50.0-55.8%)	34.0% (31.3-37.0%)	13.1% (11.1-15.3%)
IOP<6mmHg (2 consecutive visits) OR SCH, kissing choroidals, choroidals drainage	50.6% (47.7-53.7%)	45.8% (42.9-48.8%)	27.8% (25.2-30.7%)	9.3% (7.6-11.4%)
IOP<6mmHg (2 consecutive visits) WITH hypotony maculopathy	62.0% (59.2-64.9%)	56.5% (53.6-59.5%)	37.0% (34.3-40.1%)	14.8% (12.7-17.1%)
IOP<6mmHg for two weeks OR severe choroidal effusion/hemorrhage	54.4% (51.6-57.4%)	49.4% (46.5-52.4%)	31.4% (28.7-34.3%)	10.8% (9.0-12.9%)
IOP<6mmHg (2 consecutive visits after >3 months) WITH loss of ≥2 Snellen lines	60.6% (57.8-63.5%)	54.9% (52.1-58.0%)	35.9% (33.2-38.9%)	14.1% (12.1-16.4%)
IOP<6mmHg (last 2 visits) OR SCH, kissing choroidals, choroidals drainage	61.9% (59.2-64.8%)	56.3% (53.5-59.3%)	37.0% (34.2-40.0%)	14.7% (12.7-17.1%)
IOP<6mmHg for >6 months OR requiring intervention for hypotony	58.1% (55.1-61.1%)	52.6% (49.7-55.7%)	33.6% (30.9-36.6%)	12.3% (10.4-14.6%)

AC: anterior chamber; CI: confidence interval; IOP: intraocular pressure; HM: hypotony maculopathy; SCH: suprachoroidal hemorrhage

Table S10. Cox Regression Models for the risk of failure for the various literature-based hypotony failure criteria in the trabeculectomy cohort

Hypotony type (ref: no hypotony criteria)	**Criteria A Failure**		**Criteria B Failure**		**Criteria C Failure**		**Criteria D Failure**	
Trabeculectomy	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Hypotony complications	1.27 (1.20-1.33)	**<0.001**	1.26 (1.19-1.32)	**<0.001**	1.22 (1.17-1.28)	**<0.001**	1.19 (1.14-1.24)	**<0.001**
Hypotony Maculopathy	1.05 (1.03-1.07)	**<0.001**	1.05 (1.03-1.07)	**<0.001**	1.04 (1.02-1.06)	**<0.001**	1.04 (1.02-1.05)	**<0.001**
Revision for hypotony	1.07 (1.04-1.10)	**<0.001**	1.06 (1.04-1.09)	**<0.001**	1.05 (1.03-1.08)	**<0.001**	1.04 (1.02-1.07)	**<0.001**
IOP<4mmHg (any visit)	1.85 (1.71-2.00)	**<0.001**	1.83 (1.69-1.98)	**<0.001**	1.74 (1.62-1.88)	**<0.001**	1.67 (1.55-1.79)	**<0.001**
IOP<4 mmHg (any visit after >2 months)	1.26 (1.20-1.33)	**<0.001**	1.25 (1.19-1.32)	**<0.001**	1.23 (1.17-1.29)	**<0.001**	1.22 (1.16-1.27)	**<0.001**
IOP<4 mmHg (last visit)	1.06 (1.03-1.08)	**<0.001**	1.05 (1.03-1.08)	**<0.001**	1.05 (1.03-1.07)	**<0.001**	1.04 (1.03-1.06)	**<0.001**
IOP<4mmHg (2 consecutive visits)	1.34 (1.26-1.42)	**<0.001**	1.33 (1.26-1.41)	**<0.001**	1.31 (1.24-1.39)	**<0.001**	1.29 (1.22-1.36)	**<0.001**
IOP<5 mmHg (any visit)	2.58 (2.35-2.84)	**<0.001**	2.56 (2.33-2.81)	**<0.001**	2.43 (2.22-2.66)	**<0.001**	2.34 (2.14-2.55)	**<0.001**
IOP<5 mmHg (any visit after >4 weeks)	1.68 (1.57-1.81)	**<0.001**	1.67 (1.55-1.79)	**<0.001**	1.63 (1.52-1.74)	**<0.001**	1.61 (1.50-1.72)	**<0.001**
IOP<5mmHg (any visit after >3 months)	1.45 (1.36-1.54)	**<0.001**	1.44 (1.35-1.52)	**<0.001**	1.40 (1.33-1.49)	**<0.001**	1.38 (1.31-1.46)	**<0.001**
IOP<5mmHg (any visit after ≥6 months)	1.36 (1.29-1.44)	**<0.001**	1.36 (1.28-1.43)	**<0.001**	1.32 (1.26-1.39)	**<0.001**	1.30 (1.24-1.36)	**<0.001**
IOP<5mmHg (2 consecutive visits)	1.28 (1.23-1.34)	**<0.001**	1.27 (1.22-1.32)	**<0.001**	1.22 (1.17-1.26)	**<0.001**	1.17 (1.14-1.21)	**<0.001**
IOP<5mmHg (2 consecutive visits after >1 month)	1.19 (1.14-1.23)	**<0.001**	1.18 (1.14-1.22)	**<0.001**	1.15 (1.12-1.19)	**<0.001**	1.13 (1.10-1.16)	**<0.001**
IOP<5mmHg (2 consecutive visits after >3 months)	1.09 (1.05-1.12)	**<0.001**	1.08 (1.05-1.12)	**<0.001**	1.07 (1.04-1.10)	**<0.001**	1.07 (1.04-1.10)	**<0.001**

IOP<5mmHg (2 consecutive visits after >3 months or last visit)	1.18 (1.13-1.23)	**<0.001**	1.17 (1.13-1.22)	**<0.001**	1.15 (1.11-1.19)	**<0.001**	1.14 (1.10-1.18)	**<0.001**
IOP<5mmHg (last visit)	1.13 (1.10-1.17)	**<0.001**	1.13 (1.09-1.16)	**<0.001**	1.11 (1.08-1.14)	**<0.001**	1.10 (1.07-1.13)	**<0.001**
IOP<6 mmHg (any visit)	3.31 (2.99-3.67)	**<0.001**	3.29 (2.97-3.65)	**<0.001**	3.12 (2.82-3.46)	**<0.001**	2.95 (2.67-3.26)	**<0.001**
IOP<6mmHg (any visit after >1 month)	2.04 (1.88-2.21)	**<0.001**	2.02 (1.86-2.19)	**<0.001**	1.94 (1.80-2.10)	**<0.001**	1.91 (1.77-2.07)	**<0.001**
IOP<6mmHg (2 consecutive visits)	1.97 (1.82-2.14)	**<0.001**	1.96 (1.81-2.12)	**<0.001**	1.90 (1.75-2.05)	**<0.001**	1.85 (1.72-2.00)	**<0.001**
IOP<6mmHg (2 consecutive visits after >1 week)	1.82 (1.64-2.01)	**<0.001**	1.81 (1.64-2.00)	**<0.001**	1.73 (1.57-1.90)	**<0.001**	1.67 (1.53-1.82)	**<0.001**
IOP<6mmHg (2 consecutive visits after >1 month)	1.54 (1.44-1.65)	**<0.001**	1.53 (1.43-1.63)	**<0.001**	1.50 (1.41-1.60)	**<0.001**	1.48 (1.39-1.58)	**<0.001**
IOP<6mmHg (2 consecutive visits after >6 weeks)	1.47 (1.38-1.56)	**<0.001**	1.46 (1.37-1.55)	**<0.001**	1.43 (1.35-1.52)	**<0.001**	1.41 (1.33-1.49)	**<0.001**
IOP<6 mmHg (2 consecutive visits after >3 months)	1.35 (1.28-1.43)	**<0.001**	1.35 (1.27-1.42)	**<0.001**	1.32 (1.26-1.40)	**<0.001**	1.30 (1.23-1.37)	**<0.001**
IOP<6mmHg after >3 months and confirmed >1 month later	1.28 (1.22-1.35)	**<0.001**	1.28 (1.22-1.34)	**<0.001**	1.25 (1.20-1.31)	**<0.001**	1.23 (1.18-1.28)	**<0.001**
IOP<6mmHg (2 consecutive visits >6 months)	1.28 (1.22-1.35)	**<0.001**	1.28 (1.21-1.34)	**<0.001**	1.25 (1.20-1.32)	**<0.001**	1.23 (1.18-1.29)	**<0.001**
IOP<6mmHg (for >2 months)	1.33 (1.26-1.40)	**<0.001**	1.32 (1.26-1.39)	**<0.001**	1.29 (1.23-1.36)	**<0.001**	1.27 (1.21-1.32)	**<0.001**
IOP<6mmHg (2 consecutive visits for ≥2 months after >1 week)	1.33 (1.26-1.40)	**<0.001**	1.32 (1.25-1.39)	**<0.001**	1.29 (1.23-1.36)	**<0.001**	1.26 (1.21-1.32)	**<0.001**
IOP<6mmHg (2 consecutive visits ≥3 weeks apart)	1.45 (1.36-1.54)	**<0.001**	1.44 (1.36-1.53)	**<0.001**	1.40 (1.32-1.48)	**<0.001**	1.37 (1.30-1.44)	**<0.001**
IOP<6mmHg for >6 months	1.15 (1.11-1.19)	**<0.001**	1.14 (1.11-1.18)	**<0.001**	1.13 (1.09-1.16)	**<0.001**	1.11 (1.08-1.13)	**<0.001**
IOP<6mmHg (last visit)	1.18 (1.14-1.22)	**<0.001**	1.17 (1.13-1.22)	**<0.001**	1.15 (1.12-1.19)	**<0.001**	1.13 (1.10-1.17)	**<0.001**
IOP<8mmHg (last visit)	1.35 (1.29-1.41)	**<0.001**	1.34 (1.28-1.40)	**<0.001**	1.29 (1.24-1.35)	**<0.001**	1.25 (1.20-1.29)	**<0.001**

IOP<10mmHg (any visit)	10.79 (9.39-12.39)	**<0.001**	10.66 (9.28-12.25)	**<0.001**	10.44 (9.10-11.98)	**<0.001**	9.87 (8.61-11.31)	**<0.001**
IOP<4mmHg (2 consecutive visits) OR revision required	1.41 (1.33-1.50)	**<0.001**	1.40 (1.32-1.48)	**<0.001**	1.36 (1.29-1.44)	**<0.001**	1.32 (1.25-1.40)	**<0.001**
IOP<5mmHg (any visit) WITH reduced VA, shallow AC, HM, choroidals	1.72 (1.60-1.86)	**<0.001**	1.70 (1.58-1.84)	**<0.001**	1.63 (1.52-1.75)	**<0.001**	1.54 (1.44-1.64)	**<0.001**
IOP<5mmHg (any visit) WITH loss of ≥2 Snellen lines	1.68 (1.56-1.81)	**<0.001**	1.66 (1.55-1.79)	**<0.001**	1.59 (1.48-1.71)	**<0.001**	1.51 (1.41-1.61)	**<0.001**
IOP<5mmHg (2 visits) AND anatomic changes	1.09 (1.06-1.13)	**<0.001**	1.09 (1.05-1.12)	**<0.001**	1.08 (1.05-1.12)	**<0.001**	1.07 (1.04-1.11)	**<0.001**
IOP<5mmHg WITH loss of ≥2 Snellen lines (2 consecutive visits)	1.68 (1.56-1.81)	**<0.001**	1.20 (1.15-1.26)	**<0.001**	1.19 (1.14-1.24)	**<0.001**	1.17 (1.12-1.21)	**0.002**
IOP<6mmHg (any visit) WITH loss of ≥2 Snellen lines	1.87 (1.73-2.02)	**<0.001**	1.85 (1.71-2.01)	**<0.001**	1.77 (1.64-1.91)	**<0.001**	1.65 (1.54-1.77)	**<0.001**
IOP<6mmHg (any visit) WITH hypotony complications	1.13 (1.09-1.18)	**<0.001**	1.13 (1.08-1.17)	**<0.001**	1.12 (1.08-1.16)	**<0.001**	1.10 (1.07-1.14)	**<0.001**
IOP<6mmHg (any visit) WITH hypotony maculopathy	1.04 (1.01-1.06)	**0.001**	1.03 (1.01-1.05)	**0.002**	1.03 (1.01-1.05)	**0.002**	1.03 (1.01-1.05)	**0.004**
IOP<6mmHg (any visit) OR revision required	3.31 (2.99-3.67)	**<0.001**	3.29 (2.97-3.65)	**<0.001**	3.12 (2.82-3.46)	**<0.001**	2.95 (2.67-3.26)	**<0.001**
IOP<6mmHg (2 consecutive visits) WITH loss of ≥2 Snellen lines	1.28 (1.21-1.35)	**<0.001**	1.27 (1.21-1.34)	**<0.001**	1.26 (1.20-1.32)	**<0.001**	1.23 (1.17-1.28)	**<0.001**
IOP<6mmHg (2 consecutive visits) OR SCH, kissing choroidals, choroidals drainage	1.98 (1.83-2.15)	**<0.001**	1.97 (1.81-2.13)	**<0.001**	1.90 (1.76-2.06)	**<0.001**	1.86 (1.72-2.01)	**<0.001**
IOP<6mmHg (2 consecutive visits) WITH hypotony maculopathy	1.02 (1.01-1.04)	**0.011**	1.02 (1.01-1.04)	**0.011**	1.02 (1.01-1.04)	**0.011**	1.02 (1.00-1.04)	**0.014**
IOP<6mmHg for two weeks OR severe choroidal effusion/hemorrhage	1.52 (1.42-1.61)	**<0.001**	1.51 (1.42-1.61)	**<0.001**	1.47 (1.38-1.56)	**<0.001**	1.43 (1.35-1.51)	**<0.001**
IOP<6mmHg (2 consecutive visits after >3 months) WITH loss of ≥2 Snellen lines	1.13 (1.09-1.17)	**<0.001**	1.12 (1.09-1.17)	**<0.001**	1.12 (1.08-1.15)	**<0.001**	1.10 (1.07-1.13)	**<0.001**

IOP<6mmHg (last 2 visits) OR SCH, kissing choroidals, choroidals drainage	1.14 (1.10-1.18)	**<0.001**	1.14 (1.10-1.18)	**<0.001**	1.12 (1.09-1.16)	**<0.001**	1.11 (1.08-1.14)	**<0.001**
IOP<6mmHg for >6 months OR requiring intervention for hypotony	1.24 (1.19-1.30)	**<0.001**	1.24 (1.18-1.29)	**<0.001**	1.21 (1.16-1.27)	**<0.001**	1.19 (1.14-1.24)	**<0.001**

AC: anterior chamber; CI: confidence interval; IOP: intraocular pressure; HM: hypotony maculopathy; SCH: suprachoroidal hemorrhage

Table S11. Cox Regression Models for the risk of failure for the various literature-based hypotony failure criteria in the deep sclerectomy cohort

Hypotony type (ref: no hypotony criteria)	**Criteria A Failure**		**Criteria B Failure**		**Criteria C Failure**		**Criteria D Failure**	
Trabeculectomy	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Hypotony complications	1.07 (1.05-1.10)	**<0.001**	1.06 (1.04-1.08)	**<0.001**	1.04 (1.02-1.05)	**<0.001**	1.03 (1.01-1.04)	**<0.001**
Hypotony Maculopathy	1.20 (1.16-1.25)	**<0.001**	1.17 (1.13-1.21)	**<0.001**	1.11 (1.09-1.14)	**<0.001**	1.08 (1.06-1.10)	**<0.001**
Revision for hypotony	1.04 (1.02-1.06)	**<0.001**	1.04 (1.02-1.05)	**<0.001**	1.02 (1.01-1.03)	**<0.001**	1.01 (1.00-1.01)	**0.002**
IOP<4mmHg (any visit)	2.31 (2.15-2.48)	**<0.001**	2.17 (2.03-2.33)	**<0.001**	1.88 (1.77-1.99)	**<0.001**	1.66 (1.58-1.75)	**<0.001**
IOP<4 mmHg (any visit after >2 months)	1.22 (1.17-1.26)	**<0.001**	1.18 (1.14-1.23)	**<0.001**	1.11 (1.08-1.13)	**<0.001**	1.06 (1.04-1.08)	**<0.001**
IOP<4 mmHg (last visit)	1.04 (1.02-1.05)	**<0.001**	1.03 (1.02-1.05)	**<0.001**	1.02 (1.01-1.03)	**<0.001**	1.01 (1.00-1.01)	**0.002**
IOP<4mmHg (2 consecutive visits)	1.16 (1.12-1.20)	**<0.001**	1.14 (1.10-1.17)	**<0.001**	1.10 (1.08-1.13)	**<0.001**	1.08 (1.06-1.10)	**<0.001**
IOP<5 mmHg (any visit)	3.07 (2.84-3.33)	**<0.001**	2.83 (2.63-3.06)	**<0.001**	2.38 (2.22-2.54)	**<0.001**	2.04 (1.92-2.17)	**<0.001**
IOP<5 mmHg (any visit after >4 weeks)	1.40 (1.34-1.47)	**<0.001**	1.34 (1.28-1.40)	**<0.001**	1.22 (1.18-1.26)	**<0.001**	1.15 (1.12-1.19)	**<0.001**
IOP<5mmHg (any visit after >3 months)	1.32 (1.26-1.38)	**<0.001**	1.27 (1.22-1.32)	**<0.001**	1.16 (1.13-1.19)	**<0.001**	1.10 (1.08-1.13)	**<0.001**
IOP<5mmHg (any visit after ≥6 months)	1.27 (1.22-1.32)	**<0.001**	1.22 (1.18-1.27)	**<0.001**	1.13 (1.10-1.15)	**<0.001**	1.10 (1.08-1.13)	**<0.001**
IOP<5mmHg (2 consecutive visits)	1.35 (1.28-1.41)	**<0.001**	1.30 (1.25-1.36)	**<0.001**	1.23 (1.19-1.27)	**<0.001**	1.18 (1.15-1.22)	**<0.001**
IOP<5mmHg (2 consecutive visits after >1 month)	1.17 (1.13-1.21)	**<0.001**	1.15 (1.11-1.19)	**<0.001**	1.10 (1.08-1.13)	**<0.001**	1.08 (1.05-1.10)	**<0.001**
IOP<5mmHg (2 consecutive visits after >3 months)	1.12 (1.09-1.16)	**<0.001**	1.11 (1.08-1.14)	**<0.001**	1.07 (1.05-1.09)	**<0.001**	1.05 (1.03-1.06)	**<0.001**

IOP<5mmHg (2 consecutive visits after >3 months or last visit)	1.16 (1.12-1.2)	**<0.001**	1.14 (1.10-1.17)	**<0.001**	1.08 (1.06-1.11)	**<0.001**	1.05 (1.04-1.07)	**<0.001**
IOP<5mmHg (last visit)	1.06 (1.04-1.08)	**<0.001**	1.05 (1.03-1.07)	**<0.001**	1.03 (1.02-1.04)	**<0.001**	1.01 (1.01-1.02)	**<0.001**
IOP<6 mmHg (any visit)	3.84 (3.53-4.17)	**<0.001**	3.51 (3.24-3.80)	**<0.001**	2.87 (2.67-3.09)	**<0.001**	2.42 (2.27-2.59)	**<0.001**
IOP<6mmHg (any visit after >1 month)	1.62 (1.53-1.71)	**<0.001**	1.53 (1.45-1.60)	**<0.001**	1.36 (1.30-1.41)	**<0.001**	1.26 (1.22-1.31)	**<0.001**
IOP<6mmHg (2 consecutive visits)	1.58 (1.49-1.67)	**<0.001**	1.51 (1.43-1.59)	**<0.001**	1.39 (1.33-1.45)	**<0.001**	1.30 (1.25-1.35)	**<0.001**
IOP<6mmHg (2 consecutive visits after >1 week)	1.50 (1.42-1.58)	**<0.001**	1.44 (1.37-1.51)	**<0.001**	1.33 (1.28-1.38)	**<0.001**	1.26 (1.22-1.31)	**<0.001**
IOP<6mmHg (2 consecutive visits after >1 month)	1.31 (1.26-1.38)	**<0.001**	1.27 (1.22-1.32)	**<0.001**	1.19 (1.16-1.23)	**<0.001**	1.15 (1.12-1.18)	**<0.001**
IOP<6mmHg (2 consecutive visits after >6 weeks)	1.25 (1.20-1.31)	**<0.001**	1.22 (1.17-1.26)	**<0.001**	1.15 (1.12-1.18)	**<0.001**	1.11 (1.08-1.14)	**<0.001**
IOP<6 mmHg (2 consecutive visits after >3 months)	1.22 (1.17-1.26)	**<0.001**	1.19 (1.15-1.23)	**<0.001**	1.12 (1.09-1.15)	**<0.001**	1.08 (1.06-1.11)	**<0.001**
IOP<6mmHg after >3 months and confirmed >1 month later	1.19 (1.15-1.23)	**<0.001**	1.17 (1.13-1.20)	**<0.001**	1.11 (1.08-1.14)	**<0.001**	1.08 (1.06-1.10)	**<0.001**
IOP<6mmHg (2 consecutive visits >6 months)	1.17 (1.13-1.21)	**<0.001**	1.14 (1.11-1.18)	**<0.001**	1.09 (1.06-1.11)	**<0.001**	1.05 (1.04-1.07)	**<0.001**
IOP<6mmHg (for >2 months)	1.18 (1.14-1.23)	**<0.001**	1.16 (1.12-1.20)	**<0.001**	1.11 (1.09-1.14)	**<0.001**	1.08 (1.06-1.10)	**<0.001**
IOP<6mmHg (2 consecutive visits for ≥2 months after >1 week)	1.21 (1.16-1.26)	**<0.001**	1.19 (1.15-1.24)	**<0.001**	1.15 (1.11-1.18)	**<0.001**	1.12 (1.09-1.15)	**<0.001**
IOP<6mmHg (2 consecutive visits ≥3 weeks apart)	1.37 (1.30-1.44)	**<0.001**	1.33 (1.27-1.40)	**<0.001**	1.27 (1.22-1.32)	**<0.001**	1.23 (1.19-1.28)	**<0.001**
IOP<6mmHg for >6 months	1.13 (1.09-1.16)	**<0.001**	1.11 (1.08-1.15)	**<0.001**	1.08 (1.06-1.10)	**<0.001**	1.06 (1.04-1.08)	**<0.001**
IOP<6mmHg (last visit)	1.10 (1.08-1.13)	**<0.001**	1.09 (1.07-1.11)	**<0.001**	1.05 (1.04-1.07)	**<0.001**	1.03 (1.02-1.04)	**<0.001**
IOP<8mmHg (last visit)	1.27 (1.22-1.32)	**<0.001**	1.23 (1.19-1.28)	**<0.001**	1.14 (1.11-1.16)	**<0.001**	1.08 (1.06-1.09)	**<0.001**

IOP<10mmHg (any visit)	8.36 (7.62-9.17)	**<0.001**	7.66 (7.00-8.40)	**<0.001**	6.31 (5.78-6.90)	**<0.001**	5.23 (4.80-5.71)	**<0.001**
IOP<4mmHg (2 consecutive visits) OR revision required	1.18 (1.14-1.23)	**<0.001**	1.16 (1.12-1.19)	**<0.001**	1.11 (1.09-1.14)	**<0.001**	1.08 (1.06-1.11)	**<0.001**
IOP<5mmHg (any visit) WITH reduced VA, shallow AC, HM, choroidals	1.95 (1.82-2.08)	**<0.001**	1.84 (1.73-1.96)	**<0.001**	1.63 (1.55-1.71)	**<0.001**	1.48 (1.41-1.55)	**<0.001**
IOP<5mmHg (any visit) WITH loss of ≥2 Snellen lines	1.91 (1.78-2.03)	**<0.001**	1.80 (1.70-1.92)	**<0.001**	1.60 (1.52-1.69)	**<0.001**	1.46 (1.40-1.53)	**<0.001**
IOP<5mmHg (2 visits) AND anatomic changes	1.49 (1.41-1.57)	**<0.001**	1.42 (1.36-1.49)	**<0.001**	1.31 (1.26-1.36)	**<0.001**	1.24 (1.20-1.28)	**<0.001**
IOP<5mmHg WITH loss of ≥2 Snellen lines (2 consecutive visits)	1.04 (1.02-1.06)	**<0.001**	1.04 (1.02-1.05)	**<0.001**	1.03 (1.01-1.04)	**<0.001**	1.02 (1.01-1.03)	**0.002**
IOP<6mmHg (any visit) WITH loss of ≥2 Snellen lines	2.11 (1.97-2.26)	**<0.001**	1.98 (1.86-2.12)	**<0.001**	1.74 (1.64-1.83)	**<0.001**	1.56 (1.48-1.63)	**<0.001**
IOP<6mmHg (any visit) WITH hypotony complications	1.17 (1.13-1.21)	**<0.001**	1.14 (1.11-1.18)	**<0.001**	1.10 (1.07-1.12)	**<0.001**	1.07 (1.05-1.09)	**<0.001**
IOP<6mmHg (any visit) WITH hypotony maculopathy	1.06 (1.03-1.08)	**<0.001**	1.05 (1.03-1.07)	**<0.001**	1.03 (1.02-1.04)	**<0.001**	1.02 (1.01-1.03)	**<0.001**
IOP<6mmHg (any visit) OR revision required	3.84 (3.53-4.17)	**<0.001**	3.51 (3.24-3.80)	**<0.001**	2.87 (2.67-3.09)	**<0.001**	2.42 (2.27-2.59)	**<0.001**
IOP<6mmHg (2 consecutive visits) WITH loss of ≥2 Snellen lines	1.20 (1.16-1.25)	**<0.001**	1.18 (1.14-1.22)	**<0.001**	1.14 (1.11-1.17)	**<0.001**	1.10 (1.07-1.13)	**<0.001**
IOP<6mmHg (2 consecutive visits) OR SCH, kissing choroidals, choroidals drainage	1.58 (1.50-1.68)	**<0.001**	1.51 (1.43-1.59)	**<0.001**	1.39 (1.33-1.46)	**<0.001**	1.30 (1.25-1.35)	**<0.001**
IOP<6mmHg (2 consecutive visits) WITH hypotony maculopathy	1.01 (1.00-1.02)	**0.023**	1.01 (1.00-1.02)	**0.040**	1.01 (1.00-1.01)	**0.046**	1.00 (1.00-1.01)	0.10
IOP<6mmHg for two weeks OR severe choroidal effusion/hemorrhage	1.33 (1.28-1.40)	**<0.001**	1.29 (1.24-1.34)	**<0.001**	1.21 (1.17-1.25)	**<0.001**	1.16 (1.13-1.20)	**<0.001**
IOP<6mmHg (2 consecutive visits after >3 months) WITH loss of ≥2 Snellen lines	1.07 (1.05-1.10)	**<0.001**	1.06 (1.04-1.09)	**<0.001**	1.04 (1.03-1.06)	**<0.001**	1.03 (1.01-1.04)	**<0.001**

IOP<6mmHg (last 2 visits) OR SCH, kissing choroidals, choroidals drainage	1.02 (1.01-1.03)	**0.001**	1.02 (1.01-1.03)	**0.001**	1.01 (1.01-1.02)	**0.002**	1.01 (1.00-1.02)	**0.003**
IOP<6mmHg for >6 months OR requiring intervention for hypotony	1.15 (1.11-1.19)	**<0.001**	1.13 (1.10-1.17)	**<0.001**	1.09 (1.07-1.12)	**<0.001**	1.06 (1.04-1.08)	**<0.001**

AC: anterior chamber; CI: confidence interval; IOP: intraocular pressure; HM: hypotony maculopathy; SCH: suprachoroidal hemorrhage

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		Research to Prevent Blindness	Unrestricted departmental grant
		Simms/Mann Family Foundation	
		Payden Glaucoma Research Fund	Click the tab key to add additional rows.
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Manuscript Title:	Hypotony Failure Criteria in Glaucoma Surgical Studies and Their Influence on Surgery Success
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Manuscript Title:	Hypotony Failure Criteria in Glaucoma Surgical Studies and Their Influence on Surgery Success
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		Off Health spa	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☐ **None**	
		Bausch + Lomb	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☐ **None**	
		Alfa Intes srl	
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11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
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ICMJE FORM

Date:	9/17/2023
Your Name:	Alessandro Ghirardi
Manuscript Title:	Hypotony Failure Criteria in Glaucoma Surgical Studies and Their Influence on Surgery Success
US-based Author (if yes, you must fill out Open Payment section below):	NO
Manuscript Number (if known):	Click or tap here to enter text.

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ICMJE FORM

Date: 9/22/2023

Your Name: Giovanni Montesano

Manuscript Title: Hypotony Failure Criteria in Glaucoma Surgical Studies and Their Influence on Surgery Success

US-based Author (if yes, you must fill out Open Payment section below): NO

Manuscript Number (if known): Click or tap here to enter text.

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		CenterVue-iCare	
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		Omikron, SpA	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☐ **None**	
		Omikron, SpA	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
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		Relayer, LtD	

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Date: 9/17/2023

Your Name: Giacinto Triolo

Manuscript Title: Hypotony Failure Criteria in Glaucoma Surgical Studies and Their Influence on Surgery Success

US-based Author (if yes, you must fill out Open Payment section below): NO

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Manuscript Title:	Hypotony Failure Criteria in Glaucoma Surgical Studies and Their Influence on Surgery Success
US-based Author (if yes, you must fill out Open Payment section below):	YES
Manuscript Number (if known):	Click or tap here to enter text.

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Date:	9/23/2023
Your Name:	Alessandro Rabiolo
Manuscript Title:	Hypotony Failure Criteria in Glaucoma Surgical Studies and Their Influence on Surgery Success
US-based Author (if yes, you must fill out Open Payment section below):	NO
Manuscript Number (if known):	Click or tap here to enter text.

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7	Support for attending meetings and/or travel	☐ **None**	
		Bausch + Lomb	Flight, hotel reservation, and congress fee for ARVO 2023 meeting
		Thea farma spa	Flight and hotel reservation for the 2023 Moorfields International Glaucoma Symposium
		Visufarma spa	Hotel reservation and congress fee for the the Associazione per lo Studio del Glaucoma (AISG) 2023 annual meeting
8	Patents planned, issued or pending	☒ **None**	
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ICMJE FORM

Date: 9/17/2023

Your Name: Gianni Virgili

Manuscript Title: Hypotony Failure Criteria in Glaucoma Surgical Studies and Their Influence on Surgery Success

US-based Author (if yes, you must fill out Open Payment section below): NO

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8	Patents planned, issued or pending	☒ **None**	
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TITLE OF ARTICLE: Hypotony Failure Criteria in Glaucoma Surgical Studies and Their Influence on Surgery Success

AUTHORS: Alessandro Rabiolo; Giacinto Triolo; Daniela Khaliliyeh; Sang Wook Jin; Esteban Morales; Alessandro Ghirardi; Nitin Anand; Giovanni Montesano; Gianni Virgili; Joseph Caprioli; Stefano De Cillà.

AUTHOR NAME	RESEARCH DESIGN	DATA ACQUISITION AND/OR RESEARCH EXECUTION	DATA ANALYSIS AND/OR INTERPRETATION	MANUSCRIPT PREPARATION
Alessandro Rabiolo	☒	☒	☒	☒
Giacinto Triolo	☒	☒	☐	☒
Daniela Khaliliyeh	☐	☒	☐	☐
Sang Wook Jin	☐	☒	☐	☐
Esteban Morales	☐	☒	☐	☐

Alessandro Ghirardi	☐	☒	☐	☐
Nitin Anand	☐	☒	☐	☐
Giovanni Montesano	☒	☐	☒	☒
Gianni Virgili	☒	☐	☒	☐
Joseph Caprioli	☐	☒	☐	☒
Stefano De Cillà	☒	☐	☒	☒

OTHER CONTRIBUTIONS: