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Mitomycin C 0.2 mg/ml versus Mitomycin C 0.4 mg/ml during the Implantation of an Ab Externo Polystyrene-isobutylene-styrene Microshunt

A Mega-analysis

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Purpose: To compare the effectiveness and adverse event profile of standalone polystyrene-isobutylene-styrene (SIBS) microshunt implantation with adjunct mitomycin C (MMC) 0.2 mg/ml and MMC 0.4 mg/ml.

Design: Mega-analysis using individual patient data from international prospective and retrospective clinical studies.

Participants: Patients with glaucoma who underwent implantation of a SIBS microshunt with MMC as a standalone procedure.

Methods: A comparison of eyes that received MMC 0.2 mg/ml or 0.4 mg/ml.

Main Outcomes Measures: Primary outcome was complete success defined as the proportion of eyes at 1 year with all of the following: (1) no 2 consecutive intraocular pressures (IOPs) $>$ 17 mmHg; (2) no clinical hypotony; (3) $\geq$ 20% IOP reduction from baseline; and (4) no use of glaucoma medications. Secondary outcomes included IOP thresholds of 12 mmHg, 14 mm Hg, and 21 mmHg, median IOP, number of medications, risk factors for failure, interventions, adverse events, and reoperations.

Results: At 1 year, the complete success rate was significantly higher (71.3% vs. 50.46%; P $<$ 0.001) and the median IOP was significantly lower (13.0 vs 14.2 mmHg; $P < 0.05$) in the MMC 0.4 mg/ml group. Mitomycin C 0.2 mg/ml was found to be a significant risk factor for failure (hazard ratio 1.75; 95% confidence interval 1.14−2.67). Needling and surgical revision occurred at a lower rate in the MMC 0.4 mg/ml group (7% vs 18.8%; $P = 0.002$ and 4.3% vs 13.7% $P = 0.0087$, respectively). Adverse events occurred at a similar frequency in both groups (26.6% MMC 0.2 mg/ml vs 29.6% MMC 0.4 mg/ml; $P = 0.46$), most of which were early and transient.

Conclusion: Polystyrene-isobutylene-styrene microshunt implantation with MMC 0.4 mg/ml resulted in a higher success rate with greater IOP reduction compared with MMC 0.2 mg/ml. Higher MMC concentration was not associated with increased serious adverse events.

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Despite the introduction of new glaucoma surgeries in recent years, trabeculectomy remains one of the most commonly performed incisional surgeries for the management of glaucoma.[1] The use of mitomycin C (MMC) has dramatically increased the success rate of trabeculectomy,[2,3] although increasing postoperative complications.[4,5,6]

The optimal concentration, amount, and route of application of MMC in trabeculectomy have been studied and debated.[3,7,8] Some studies have suggested that a higher concentration of intraoperative MMC may be associated with increased success rates in trabeculectomy.[3,9] The use of MMC could also improve the surgical results of microinvasive bleb surgeries (MIBS) that promote the formation of a filtering bleb.[10,11]

The PRESERFLO microshunt (Santen) is an 8.5 mm length and 70-micron lumen bleb-forming external MIBS device. The creation of a filtering bleb through the microshunt and under the conjunctiva lowers intraocular pressure (IOP) by bypassing aqueous humor's natural outflow pathway. Furthermore, the microshunt is composed of polystyrene-isobutylene-styrene (SIBS), a material with excellent biocompatibility, which has been found to induce

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minimal inflammation and capsular tissue formation, reducing the amount of collagen deposition and myofibroblast differentiation when compared to silicone.[12,13] The main advantage of this device is the ability to minimize hypotony while forming a posterior bleb with potentially improved morphology.[14,15] This potentially safer design may allow for greater MMC dose use to address episcleral fibrosis, the main cause of bleb failure.

The use of MMC has been advocated in MIBS, although there is little evidence regarding the ideal dose, concentration, and route of administration. In the last few years, studies evaluating the SIBS microshunt implantation with MMC have shown variable surgical outcomes, with some hypothesizing that higher concentrations of MMC could be associated with higher success rates.[14–17] A prospective, randomized study evaluated the success of SIBS microshunt implantation in association with MMC 0.2 mg/ml, and a surgical success rate of 53.9% was found after 1 year of follow-up.[10] Other studies using higher concentrations of MMC have found higher success rates.[14,17,18]

The lack of consensus on the most effective concentration of MMC during the implantation of MIBS highlights an area where further studies are needed. As opposed to a more simplistic meta-analysis of published summary data, we were able to obtain, format, code, and analyze individual raw patient data from 4 large multicenter studies into a mega-analysis. This study aimed to compare the surgical success and adverse event profile of the SIBS microshunt implanted with a lower MMC dose (0.2 mg/ml) compared with that of the SIBS microshunt implanted with a higher dose of MMC (0.4 mg/ml).

Methods

This is a 1-year mega-analysis from 3 prospective and 1 retrospective international clinical studies of eyes undergoing MIBS with a SIBS microshunt and MMC. Data were obtained and analyzed from 37 clinical centers located in Canada, USA, France, Italy, Dominican Republic, Netherlands, Spain, United Kingdom, and Switzerland. Institutional Review Board/Ethics Committee approval and patient consent was obtained for all the primary studies and additional Institutional Review Board approval was received from Trillium Health Partners for this study, which adhered to the tenets of the Declaration of Helsinki.

Data Source

Our study design consists of a mega-analysis that can also be described as a meta-analysis of individual participant data, which analyzes a combination of raw patient data from different studies with comparable conditions. The raw data were pooled from 4 publications: the US trial,[10] the European trial,[15] the Dominican Republic trial,[18] and the Canadian trial.[16] The US trial (NCT01881425) was a prospective, single-masked, randomized, multicenter, noninferiority study that compared the effectiveness and safety of standalone SIBS microshunt vs. trabeculectomy in patients with primary open-angle glaucoma (POAG).[10] We included data only from the SIBS microshunt group in our analysis. The European trial (NCT02177123) was a prospective, single-arm, multicenter study that evaluated the safety and efficacy of standalone SIBS microshunt in patients with POAG.[15] The Dominican Republic trial (NCT00772330) was a prospective, nonrandomized, single-arm, interventional study that evaluated the SIBS microshunt standalone or in combination with cataract surgery.[18] The Canadian trial was a retrospective, consecutive, interventional case series that evaluated the efficacy and safety of SIBS microshunt standalone or combined with cataract surgery in patients with glaucoma with or without previous subconjunctival surgery.[16] Details of each study design have been previously described, and a summary of study designs, number of participants, number of centers, and details about the MMC application can be found in Table 1.[10,15,16,18] Although our primary studies have different sample sizes and designs, the impact of these differences was minimized as we collected the raw individual patient data from those 4 different studies. This permitted us to apply uniform inclusion and exclusion criteria directly to individual patient data, ensuring a more consistent and appropriate basis for pooling and creating a new cohort of patients.

Inclusion and Exclusion Criteria

Patients aged $\geq$ 30 years old with POAG, combined mechanism glaucoma, normal pressure glaucoma, pigmentary glaucoma, pseudoexfoliative glaucoma with IOP $\geq$ 18 mmHg on maximally tolerated medical therapy and who underwent implantation of the SIBS microshunt with MMC as a standalone procedure in each of the 4 clinical trials were included in the analysis. Eyes with other types of glaucoma were excluded. Eyes that had the procedure combined with phacoemulsification or had prior incisional filtering glaucoma surgery, suprachoroidal stent, retinal surgery, corneal graft surgery, or cyclophotocoagulation were also excluded. Patients who underwent microshunt implantation with a MMC concentration other than 0.2 mg/ml or 0.4 mg/ml or eyes with $<$ 1 month of follow-up were excluded.

Microinvasive Bleb-forming Surgery with Microshunt Implantation and Postoperative Management

The procedure for microshunt implantation and postoperative management was similar among all the 4 trials and has been previously described.[10,15,16,18]

Mitomycin C Dosing

For all studies, MMC was applied using MMC-soaked sponges under a conjunctival flap on bare sclera. The decision on which concentration would be used was based either on the study protocol or the surgeon's preference (Table 1). For the US trial, the MMC concentration, based on the study protocol, was 0.2 mg/ml for 2 minutes. In the Dominican Republic trial, the MMC concentration was 0.4 mg/ml for 3 minutes. For the European trial, the MMC concentration varied between centers and was decided based on the site's preference. For the Canadian trial, patients received progressively higher doses of MMC in a time interrupted fashion over the study period. Initial dosing was 0.2 mg/ml for 2 minutes followed by 0.4 mg/ml for 2 minutes for the next cohort.

Primary Outcome

The proportion of eyes achieving surgical success at 1 year was the primary outcome. Complete success was defined by all of the following criteria: (1) no 2 consecutive IOP readings $>$17 mmHg; (2) no clinical hypotony (defined as: IOP $<$ 6 mmHg with a loss of $>$ 2 lines of vision); (3) $\geq$ 20% IOP reduction from the IOP at the time the decision was made to undergo surgical intervention (decision IOP); and (4) no use of glaucoma medications. Qualified

Table 1. Summary of Study Designs and Mitomycin C Application

Study	Study Design	Number of Centers	Number of Eyes	Eyes Included in Our Analysis	MMC Dosing
US trial[10]	Prospective, single-masked, randomized, multicenter, noninferiority	29	395	273	0.2 mg/cc for 2 minute
European trial[15]	Prospective, single-arm, multicenter	6	107	78 36 eyes (MMC 0.2) 46 eyes (MMC 0.4)	3 sites: 0.2 mg/cc (2 sites for 2 minutes and 1 site for 3 minutes) 2 sites: 0.4 mg/cc (1 site each for 2 or 3 minutes) 1 site used 0.28 mg/cc for 2 minutes
Dominican Republic trial[19]	Single-center, nonrandomized, single-arm, interventional clinical	1	23	14	0.4 mg/cc for 3 minutes
Canadian trial[16]	Retrospective, consecutive, interventional case series	1	436	85 24 eyes (MMC 0.2) 52 eyes (MMC 0.4)	0.2, 0.4 or 0.5 mg/cc for 2 minutes. Time-based decision*

*The mitomycin c (MMC) dosing was increased as surgeons became increasingly comfortable with the microshunt bleb morphology. Initially, the blebs were found to be posterior with minimal avascularity, leading to an increase in MMC concentration from 0.2 mg/ml to 0.4 mg/ml and 0.5 mg/ml.

success permitted the use of glaucoma medications. Loss of light perception or surgical reoperations for glaucoma were defined as immediate failures. Within the first 3 postoperative months, IOP outside threshold, and use of glaucoma medication were not regarded as failures. Instances of in-clinic postoperative interventions, such as needling, were not regarded as failures at any point during follow-up.

Secondary Outcomes

Secondary efficacy outcome measures included IOP thresholds of 12 mmHg, 14 mm Hg, and 21 mm Hg for complete and qualified success criteria with 20% IOP reduction from baseline. Median IOP and medication number were also compared. We also investigated potential risk factors for failure, including sex, age, ethnicity, right vs. left eye, lens status, history of trabeculoplasty, glaucoma type, glaucoma severity, decision IOP, preoperative vision, diabetes status, and MMC dose.

Safety Outcomes

Minor adverse events (including conjunctival leak or dehiscence, hyphema, vitreous hemorrhage, choroidal detachments, macular folds, prolonged inflammation, corneal decompensation, macular edema, diplopia, iris incarceration, or blocked microshunt), serious adverse events (including acute angle closure, exposed microshunt, retinal detachment, suprachoroidal hemorrhage, malignant glaucoma, blebitis, endophthalmitis, or loss of light perception), interventions during the postoperative period, and reoperations for glaucoma were recorded and analyzed as potential risk factors.

Statistical Analysis

SAS university edition software was used to conduct all statistical analyses (SAS Institute Inc). Graphs were created using Prism 9 or SAS university edition software (Version 9.1.2, GraphPad Software). Categorical variables were represented as proportions, and the Fisher exact test was used to compare treatment groups. Continuous outcomes were described as means (standard deviation) or medians (interquartile range [IQR]), depending on the distribution of the data, and then compared using Wilcoxon tests or 2-sided *t*-tests, as indicated by normality. Logarithm of the minimum angle of resolution conversions were made for all Snellen visual acuity measures. For each IOP threshold, survival analysis for complete and qualified success was calculated and displayed in Kaplan-Meier curves. Log-rank tests were performed to compare survival between the 2 treatment groups.

This study aggregated individual patient data from 4 different trials. A one-stage meta-analytic approach was employed using Cox proportional hazard models. The aggregation of individual patient level data across 4 studies of varying designs was expected to result in heterogeneity, thus a nested random effects model was employed to combine the data.[20] Further, some patients within trials had both eyes enrolled or came from the same surgical site, as such we accounted for this intracluster dependence using a nested frailty model by trial, site, and eye, employing the approach popularized by Lee, Wei, and Amato (1992),[21] which estimates the regression parameters in the Cox model by maximum partial likelihood estimates under an independent working assumption and employs a robust sandwich covariance matrix estimate. In short, frailty terms were added to the random effects models in a nested structure to account for differences in magnitude of baseline hazard functions between patient clusters formed by trial, surgical site, and eye. Statistical significance was defined as a 2-sided P value < 0.05.

The following variables were examined on a univariable (crude) and multivariable (adjusted) basis: age, sex, eye, phakic status, disease severity, ethnicity, decision IOP, MMC dose, type of glaucoma, and diabetes diagnosis. To approximate data with equivalent failure intervals, the Efron method was used. No competing risk factors were believed to have the potential to affect data censoring. Regression analysis with a condition index cutoff of > 30 was used to estimate collinearity. To ascertain if the conditions for proportional hazards were satisfied for each variable, Martingale residuals were used. If this presumption was violated, it was addressed by stratifying the model according to the nonproportional variable or by including a time-variable interaction term. The time-variable interaction term was excluded from the final model if the regression coefficient indicated that it only contributed $\leq 1\%$ to the change in hazard over time.

Table 2. Baseline Characteristics

Characteristics	Total	MMC 0.2	MMC 0.4	*P* Value
Eyes, n	450	335	115	
Demographic				
Age (yrs); median (IQR)	65 (58-72)	66 (59-72)	61 (53-71)	0.002
>70 yrs old, n (%)	133 (29.5)	104 (31)	29 (25)	0.29
Left eye, n (%)	213 (47.3)	153 (45.7)	60 (52.2)	0.24
Female, n (%)	233 (51.8)	185 (55.2)	48 (41.7)	0.01
Diabetes, n (%)	77 (17.1)	66 (19.7)	11 (9.6)	0.01
Ethnicity, n (%)				
White	242 (53.8)	211 (63)	31 (26.9)	0.0001
Non-White	208 (46.2)	124 (37)	84 (73.1)	0.0001
Vision				
Preoperative VA (logMAR), median (IQR)	0.18 (0.1-0.3)	0.18 (0.1-0.3)	0.18 (0.1-0.3)	0.58
Preoperative BCVA 0.4 logMAR or worse, n(%)	16 (3.5)	5 (1.5)	11 (9.6)	0.0003
Decision IOP, median (IQR)*	21 (19.3-25.0)	21.3 (19.5-25.2)	20.5 (19-24)	0.09
Decision medication classes, median (IQR)*	3 (2-4)	3 (2-4)	3 (2-3)	0.001
Glaucoma type and severity				
Disease type, n (%)				
Primary open-angle	441 (98)	329 (98.2)	112 (97.4)	0.69
Pseudoexfoliative	6 (1.3)	4 (1.2)	2 (1.8)	0.64
Pigment dispersion	3 (0.7)	2 (0.6)	1 (0.8)	0.99
Cup-to-disc ratio, med (IQR)	0.8 (0.7-0.9)	0.8 (0.7-0.9)	0.85 (0.7-0.9)	0.13
Preoperative MD, median (IQR)	−11 (−17.9 to −5.8)	−10.5 (−17.3 to −6)	−12.3 (−19.4 to −5)	0.71
Disease severity, n (%)†				
Mild	130 (28.9)	94 (28.1)	36 (31.3)	0.55
Moderate	117 (26)	95 (28.4)	22 (19.1)	0.06
Severe	203 (45)	146 (43.6)	57 (49.6)	0.28
Previous ocular laser/surgery, n (%)				
Canal surgery	9 (2)	5 (1.5)	4 (3.5)	0.24
Cataract surgery	181 (40.2)	142 (42.4)	39 (33.9)	0.12
Laser trabeculoplasty	50 (11.1)	13 (3.9)	37 (32.2)	0.0001
Trabeculotomy/trab. Stents	27 (6)	21 (6.3)	6 (5.2)	0.82

BCVA = best-corrected visual acuity; IOP = intraocular pressure; IQR = interquartile range; logMAR = logarithm of the minimum angle of resolution; MD = mean deviation (dB); MMC = mitomycin C; SD = standard deviation; VA = visual acuity.
*At which time the decision was made to proceed with surgery.
†Based on mean deviation on visual fields: mild, 0 dB to more than −6 dB; moderate, −6 dB to more than −12 dB; advanced, −12 dB or worse.

Results

Study Population and Baseline Characteristics

This study identified 984 eyes that underwent SIBS microshunt implantation with MMC. From this sample, 526 eyes were excluded from the analysis for the following reasons: had the procedure combined with phacoemulsification or were nonopen angle glaucoma (primary angle closure, uveitic, traumatic, elevated episcleral venous pressure, or neovascular), had other MMC concentration other than 0.2 or 0.4 mg/ml or had less than 1 month of follow-up. Eight eyes had less than 1-month follow-up and were also excluded from the analysis. A total of 450 eyes of 441 patients were included in the final study cohort, including 335 eyes that underwent standalone SIBS microshunt implantation with MMC 0.2 mg/ml and 115 eyes that underwent the same procedure with MMC 0.4. mg/ml. The 1-year follow-up rate was 97.1% and 94.8% in the MMC 0.2 mg/ml and the MMC 0.4 mg/ml groups, respectively ($P > 0.05$). The baseline characteristics of all included eyes are summarized in Table 2. Overall, the demographic and key ocular baseline characteristics were similar between groups. However, a number of baseline characteristics were significantly different between groups (sex, age, diabetes, ethnicity, vision and number of medications preoperatively, and previous history of trabeculoplasty).

Primary Outcome

Complete success for the primary IOP threshold of 6 to 17 mmHg occurred in 50.6% of eyes in the MMC 0.2 mg/ml group and in 71.3% of eyes in the MMC 0.4 mg/ml group ($P < 0.0001$). For qualified success, surgical success improved to 79.6% and 89.6% ($P < 0.01$) in the MMC 0.2 mg/ml and 0.4 mg/ml group, respectively. The unadjusted Kaplan-Meier survival curves for the IOP thresholds of 6 to 12 mmHg, 6 to 14 mmHg, 6 to 17 mmHg, and 6 to 21 mmHg for complete and qualified success for each group are presented in Figure 1A−H. For complete success criteria for the primary IOP threshold of 6 to 17 mmHg, the median (IQR) time to failure was 5.9 (IQR 3.8−9.0) months (n = 165) in the MMC 0.2 mg/ml group and 8.7 (IQR 6.0−10.4) months (n = 33) in the MMC 0.4 mg/ml group. Three failures occurred due to clinical hypotony in the MMC 0.2 mg/ml group and none in the 0.4 mg/ml group. Reasons for treatment failure at the primary outcome for complete success are shown in Table 3.

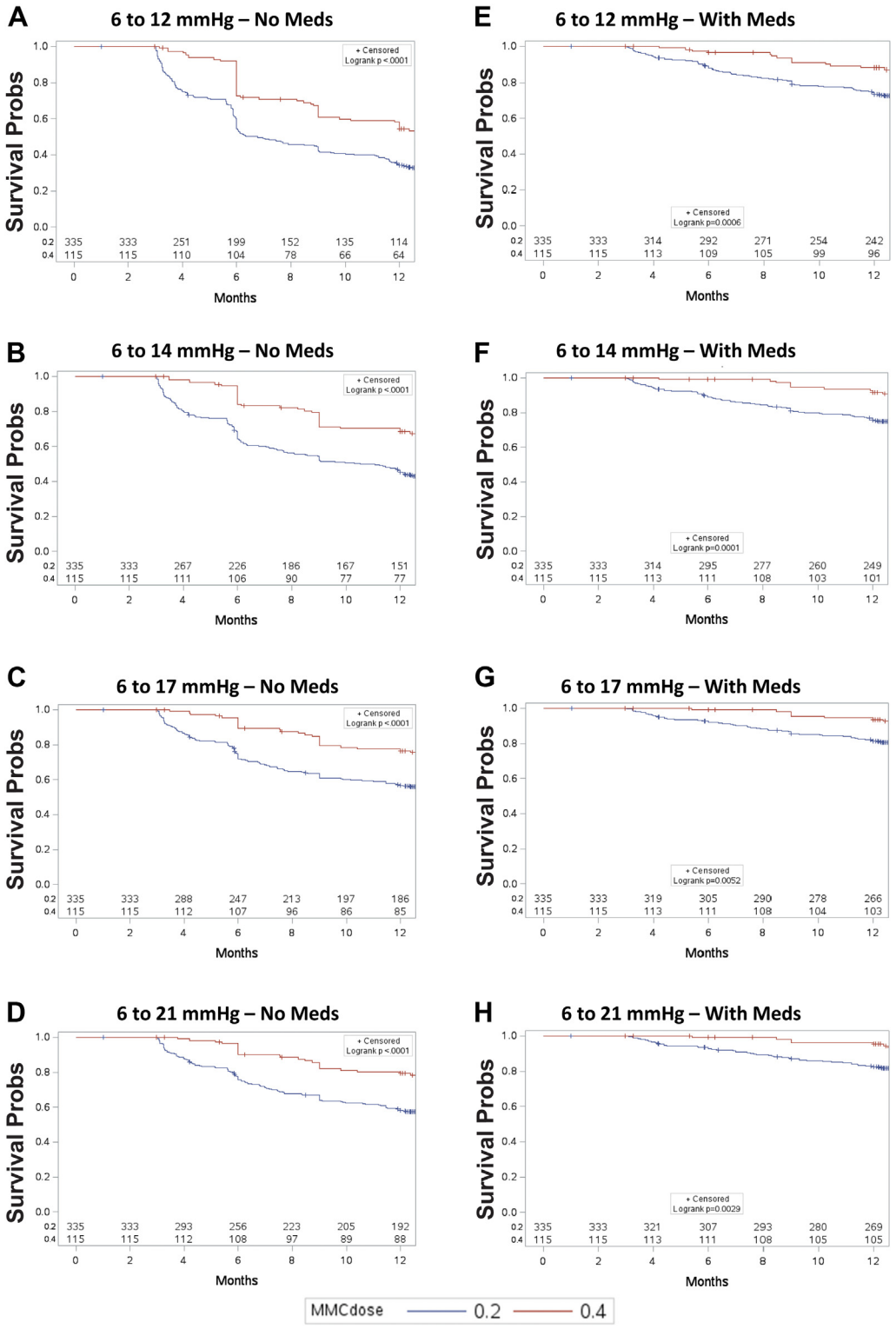

Figure 1. Kaplan-Meier survival curves for complete and qualified success through 12 months for each group. Kaplan-Meier survival curves for complete success defined as eyes being medication free, achieving a ≥20% intraocular pressure (IOP) reduction, and no 2 IOP measurements above (**A**) 12 mmHg, (**B**) 14 mmHg, (**C**) 17 mmHg, (**D**) 21 mmHg without clinical hypotony. (**E**–**H**) Qualified success. Number at risk for each timepoint is indicated just above the x-axis.

Table 3. Reasons for Treatment Failure at the Primary Outcome for Complete Success

Reason for Failure, n (%)	MMC 0.2 (n = 166)	MMC 0.4 (n = 33)
IOP >17 mmHg*	107 (64.5)	16 (48.5)
<20% IOP reduction*	20 (12)	6 (18.2)
Persistent hypotony†	3 (1.8)	-
Revision/reoperation for glaucoma	4 (2.4)	2 (6.1)
Loss of light perception	-	-
Medication administration	32 (19.3)	9 (27.3)

IOP = intraocular pressure; MMC = mitomycin C.
*Intraocular pressure (IOP) > 17 mmHg or not reduced by 20% from time of surgical decision-making, on 2 consecutive follow-up visits after 1 month.
†IOP <6 mmHg with 2 or more lines of vision loss from baseline, on 2 consecutive follow-up visits after 1 month.

Secondary Intraocular Pressure Outcomes

For the IOP threshold of 12 mmHg, complete success in the MMC 0.2 mg/ml group and MMC 0.4 mg/ml group was 23.7% and 49.6%, respectively ($P < 0.0001$); and qualified success was 70.1% and 82.6%, respectively ($P = 0.0006$). For the IOP threshold of 14 mmHg, complete success in the MMC 0.2 mg/ml group and MMC 0.4 mg/ml group was 36.8% and 59.1%, respectively ($P < 0.0001$); and qualified success was 73.1% and 87.8%, respectively ($P = 0.0003$). For the IOP threshold of 21 mmHg, complete success in the MMC 0.2 mg/ml and 0.4 mg/ml was 52.1% and 73.0%, respectively ($P < 0.0001$); and qualified success was 80.8% and 91.3%, respectively ($P = 0.0054$).

Risk Factors for Surgical Failure

For the regression analysis identifying risk factors for failure (Fig 2), the strictest criteria (IOP threshold 6−14 mmHg with ≥ 20% IOP reduction from baseline) for the greatest statistical power was used. Eyes receiving an intraoperative MMC dose of 0.2 mg/ml (univariate hazard ratio [HR] 1.76; 95% confidence interval [CI] 1.17−2.65; and multivariate HR 1.75; 95% CI 1.14−2.67), non-White status (univariate HR 1.65; 95% CI 1.23−2.20; and multivariate HR 1.40; 95% CI 1.02−1.89), each additional medication class at baseline (univariate HR 1.18; 95% CI 1.06−1.32; and multivariate HR 1.13; 95% CI 1.02−1.27), and a baseline IOP ≥ 21 mmHg (univariate HR 1.31; 95% CI 1.03−1.68; and multivariate HR 1.34; 95% CI 1.04−1.72) were associated with an increased risk of failure. Left eye, female sex, diabetes, age < 70 years, mean deviation < −12 dB on visual field testing, and pseudophakia were not found to be risk factors for failure.

Intraocular Pressure and Medication Use

Median IOP and medication use are shown in Figure 3. At 1 year, the median IOP in the MMC 0.2 mg/ml group decreased from 21.3 mmHg (IQR 19.5−25.1 mmHg) at baseline to 14.2 mmHg (IQR 11.8−16.5 mmHg) at 1 year (33.3% reduction, $P < 0.0001$). The median IOP in the MMC 0.4 mg/ml group decreased from 20.5 mmHg (IQR 19.0−24.8 mmHg) at baseline to 13.0 mmHg (IQR 11−15.9 mmHg) at 1 year (36.6% reduction, $P < 0.0001$). When comparing the 2 groups, the MMC 0.4 mg/ml group had a significantly lower median IOP at all postoperative visits (3 months $P < 0.0001$, 6 months $P < 0.01$, 9 months $P < 0.05$, and 1 year

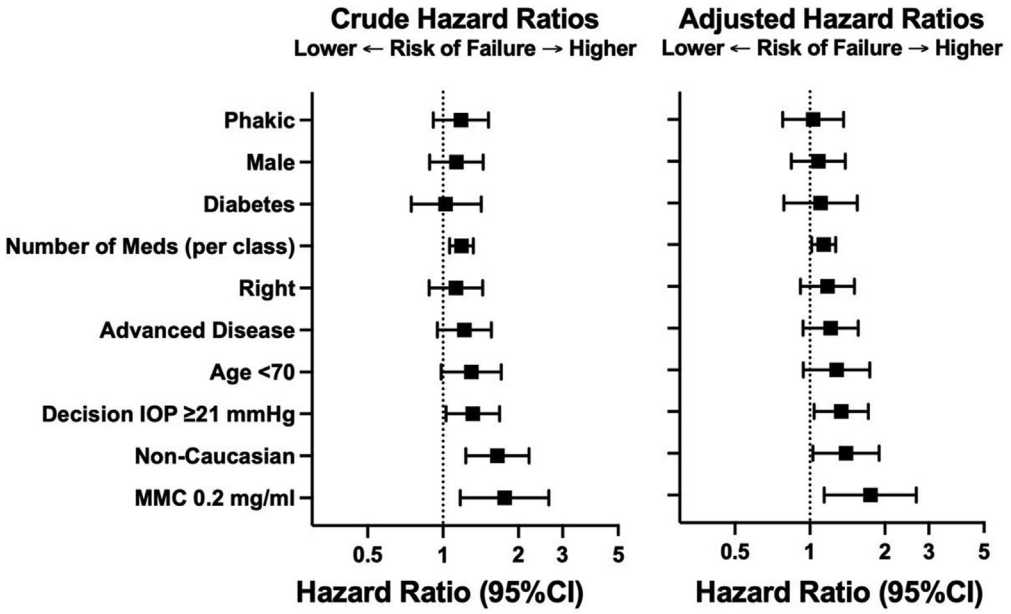

Figure 2. Crude and adjusted hazard ratios for surgical failure. Shown are crude (left) and adjusted (right) hazard ratios for various risk factors, with 95% confidence intervals. Decision IOP: intraocular pressure at the time surgery was decided. Number of Meds: number of glaucoma medication classes pre-operatively. Advanced disease was defined as a mean deviation on visual fields worse than −12 dB. MMC = mitomycin C; POAG = primary open-angle glaucoma.

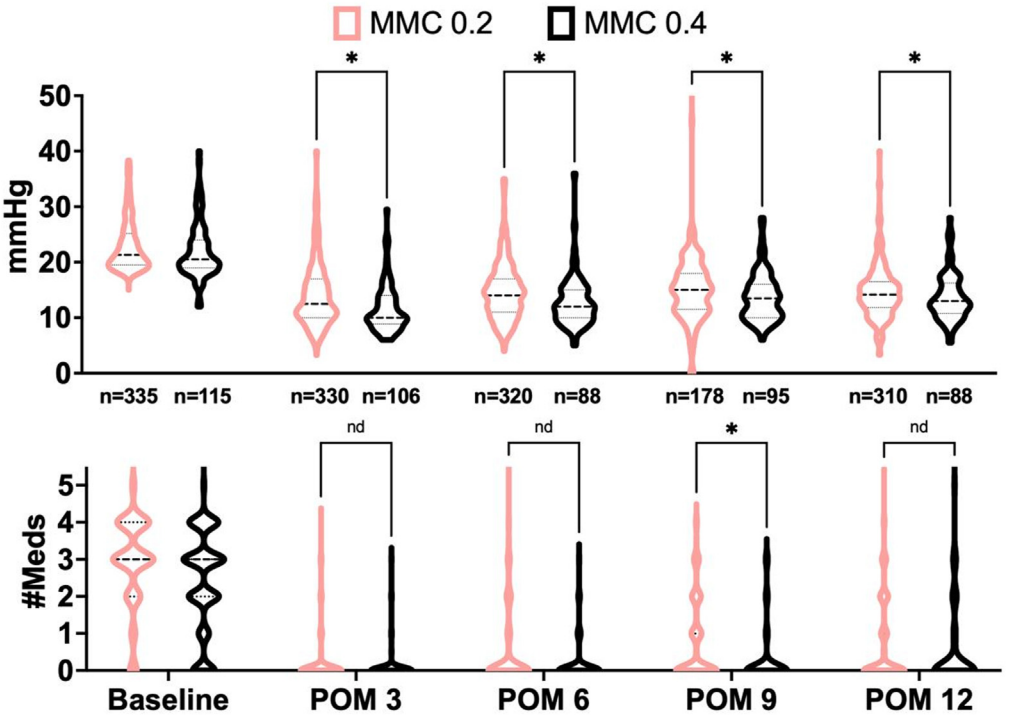

Figure 3. Violin plots with median and interquartile ranges of intraocular pressure and medication classes at the time the decision was made to undergo surgery and at the indicated follow-up visit for each group. POM = postoperative month. Width of the violin plots represents the proportion of eyes at a given y-value at each follow-up visit.

Table 4. Early and Late Postoperative Adverse Events

Complication	MMC 0.2 (n = 335)			MMC 0.4 (n = 115)		
	Total	*Early(<3 mos)*	*Late(>3 mos)*	*Total*	*Early(<3 mos)*	*Late(>3 mos)*
Minor, n (%)						
Bleb encapsulation	27 (8.1)	27 (8.1)		6 (5.2)	6 (5.2)	
Shallow AC	22 (6.6)	18 (5.4)	7 (2.1)	6 (5.2)	5 (4.3)	1 (0.9)
Choroidal	17 (5.1)	14 (4.2)	3 (0.9)	6 (5.2)	5 (4.3)	3 (2.6)
Hyphema	18 (5.4)	17 (5.1)	3 (0.9)	7 (6.1)	7 (6.1)	
Iritis	13 (3.9)	11 (3.3)	3 (0.9)	1 (0.9)		1 (0.9)
Diplopia	1 (0.3)		1 (0.3)	1 (0.9)	1 (0.9)	
Ptosis	12 (3.6)		12 (3.6)	3 (2.6)		3 (2.6)
Iris-tube touch	8 (2.4)	5 (1.5)	5 (1.5)	5 (4.3)	5 (4.3)	1 (0.9)
Dellen	2 (0.5)	2 (0.5)		2 (1.7)	1 (0.9)	1 (0.9)
Epithelial defect	1 (0.3)		1 (0.3)	2 (1.7)	2 (1.7)	
Leak/dehiscence	2 (0.5)		2 (0.5)	2 (1.7)	2 (1.7)	
Macular edema	3 (0.9)		3 (0.9)			
Tube migration	2 (0.5)		2 (0.5)	1 (0.9)		1 (0.9)
Corneal Edema	1 (0.3)	1 (0.3)	1 (0.3)			
Cornea-tube touch	1 (0.3)		1 (0.3)			
Hypot. maculopath	1 (0.3)		1 (0.3)			
Iridocorneal touch	1 (0.3)	1 (0.3)				
Vitreous Hemorrhage	1 (0.3)	1 (0.3)				
Major, n (%)						
Tube erosion	1 (0.3)		1 (0.3)			
Malignant glaucoma	1 (0.3)	1 (0.3)				
Suprachoroidal hemorrhage				1 (0.9)		1 (0.9)
Retinal detachment	1 (0.3)		1 (0.3)			

AC = anterior chamber; MMC = mitomycin C.

Table 5. Postoperative Interventions

Intervention, n (%)	MMC 0.2 (n = 335)	MMC 0.4 (n = 115)	Odds Ratio (95%CI)
Any intervention	91 (27.2)	13 (11.3)	0.34 (0.18-0.63)
Needling	63 (18.8)	8 (7)	0.32 (0.15-0.67)
AC tap	12 (3.6)	1 (0.9)	0.23 (0.02-1.53)
5-FU injection	10 (2.9)	-	-
Laser to ostomy	8 (2.4)	-	-
AC reformation	3 (0.9)	1 (0.9)	0.97 (0.07-6.56)
MMC injection	1 (0.3)	-	-
Choroidal drainage	1 (0.3)	-	-

AC = anterior chamber; CI = confidence interval; MMC = mitomycin C.

$P < 0.05$). The medication use was significantly lower in the MMC 0.4 mg/ml group compared to the MMC 0.2 mg/ml group at postoperative month nine ($P < 0.001$), but no significant difference was noted at any other postoperative timepoint. Median medication count at 1-year follow-up was 0 (IQR 0−1) for the MMC 0.2 mg/ml group, and 0 (IQR 0 to 0) for the MMC 0.4 mg/ml group ($P = 0.23$). At 1-year, 63.4% and 75% eyes were medication free in the MMC 0.2 mg/ml and 0.4 mg/ml groups, respectively ($P < 0.05$).

Postoperative Adverse Events and Interventions

Table 4 shows early and late postoperative adverse events over a 1-year period. Eighty-nine eyes (26.6%) in the MMC 0.2 mg/ml group and 34 eyes (29.6%) in the MMC 0.4 mg/ml group had minor adverse events, which were not significantly different ($P = 0.46$). In total, there were 175 distinct minor adverse events that occurred within the MMC 0.2 mg/ml group vs. 38 distinct adverse events in the MMC 0.4 mg/ml group.

Early adverse events occurred in 54 eyes (16.1%) in the MMC 0.2 mg/ml group and in 21 eyes (18.3%) in the MMC 0.4 mg/ml group ($P = 0.66$). Late adverse events, occurring 3 months or more postoperatively, occurred in 51 eyes (15.2%) in the MMC 0.2 mg/ml group and in 17 eyes (14.8%) in the MMC 0.4 mg/ml group ($P = 0.76$). In total, there were 70 early and 105 late adverse events in the MMC 0.2 mg/ml group, with 36 early and 43 late adverse events in the MMC 0.4 mg/ml group.

Hypotony related adverse events such as choroidal detachment (5.1% vs. 5.2.% $P > 0.99$) and hypotony maculopathy (0.3% vs. 0%) occurred at a similar frequency in both groups. One patient with choroidal detachment required choroidal drainage in the MMC 0.2 mg/ml group. All the others choroidal detachments resolved with conservative management. Bleb encapsulation was the most common complication (8.1% vs. 5.2%, $P = 0.41$). Regarding serious adverse events, there was 1 case of tube erosion (0.3%), retinal detachment (0.3%) and malignant glaucoma (0.3%) in the MMC 0.2 mg/ml group, and 1 case of suprachoroidal hemorrhage (0.9%) in the MMC 0.4 mg/ml group. No cases of endophthalmitis occurred in either group.

Through 1-year of follow-up, 91 (27.2%) eyes in the MMC 0.2 mg/ml group and 13 (11.3%) eyes in the MMC 0.4 mg/ml group required a postoperative intervention ($P = 0.0003$), as summarized in Table 5. Needling was the most common intervention performed, which occurred in a higher percentage of eyes in the MMC 0.2 mg/ml group (18.8% vs. 7% P=0.002). The median (IQR) time to needling was 4.0 (IQR 1.9−6.8) months and 4.2 (IQR 2.7−7.7) months in the MMC 0.2 mg/ml and 0.4 mg/ml groups, respectively, as shown in Figure 4.

Revisions and Reoperations

Revisions and reoperations are summarized in Table 6.

Eyes in the MMC 0.2 mg/ml group underwent an open bleb revision more often than in MMC 0.4 mg/ml group (13.7% vs.

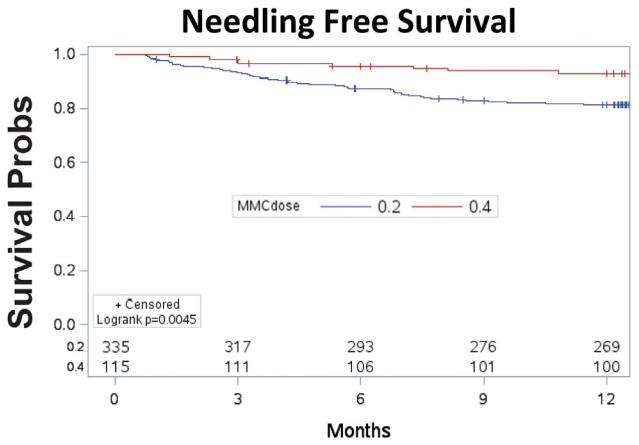

Figure 4. Kaplan-Meier survival curve for postoperative needling for each group.

Table 6. Postoperative Revisions and Reoperations

Procedure, n (%)	MMC 0.2 (n = 335)	MMC 0.4 (n = 115)	Odds Ratio (95%CI)
Any revision	46 (13.7)	5 (4.3)	0.29 (0.12–0.72)
Ab externo bleb revision	43 (12.8)	3 (2.6)	
Device reposition	5 (1.5)	1 (0.9)	
Flap revision	-	1 (0.9)	
Any reoperation	29 (8.7)	9 (7.8)	0.89 (0.41–1.87)
Tube shunt	21 (6.3)	9 (7.8)	
Trabeculectomy	7 (2.1)	-	
MIBS	-	2 (1.7)	
CPC	3 (0.9)	-	
Canaloplasty	1 (0.3)	-	

CI = confidence interval; MIBS = minimally invasive bleb surgery; MMC = mitomycin C; Tube shunt = Ahmed Glaucoma Valve, Baerveldt Glaucoma Valve, or Molten Glaucoma Drainage Device.

4.3%, $P = 0.0087$). Reoperation was defined as undergoing another glaucoma procedure and occurred in 29 eyes (8.7%) in the MMC 0.2 mg/ml group and 9 eyes (7.8%) in the MMC 0.4 mg/ml group ($P = 0.85$).

Discussion

Variable results have been published on SIBS microshunt and MMC dosing, with a paucity of recommendations on the optimal dose of MMC to increase surgical success while not increasing complication rates. This study represents a mega-analysis of individual patient data combined from international clinical studies of eyes undergoing stand-alone SIBS microshunt implantation with MMC 0.2 mg/ml and 0.4 mg/ml. It is the largest study to date comparing 2 MMC concentrations on SIBS microshunt implantation with excellent follow-up rate. Our results showed, at post-operative year 1, a benefit in combining SIBS microshunt implantation with MMC 0.4 mg/ml. The higher dose of MMC was associated with a higher success rate, greater IOP reduction, reduced needling rate, and need for postoperative revision.

Treatment success was subdivided into complete and qualified based on the need for supplemental medical therapy and both were significantly higher in the MMC 0.4 mg/ml group for all IOP thresholds (12, 14, 17, and 21 mmHg). Previous studies also showed that a higher concentration of MMC in SIBS microshunt implantation increased success rates and decreased needling rates.[14–17] The most common postoperative intervention in this study was needling, with lower rates in the MMC 0.4 mg/ml group (18.8% vs. 7%; $P = 0.002$). Previous publications showed needling rates varying between 8% and 19%,[14–19] with higher frequency when a lower concentration of MMC (0.2 mg/ml) was used.[14,16] Bleb revision was significantly more frequent in the MMC 0.2 mg/ml group. Eyes in the MMC 0.4 mg/ml group were approximately twice as likely to be medication free (odds ratio: 0.59, 95% CI 0.37–0.97) when compared to the MMC 0.2 mg/ml group at 1 year, which may provide benefit on compliance, medication adverse events and patient's quality of life.[22,23,24]

The use of MMC has dramatically increased the success rates of trabeculectomy, although this has come at the cost of an increased risk of postoperative complications.[25–28] Considerable basic science and clinical research have been done to determine the optimal dose and exposure time of MMC in glaucoma surgery, and it was demonstrated that fibroblast inhibition induced by MMC depends mainly on its concentration rather than the duration of exposure.[9,29,30,31] A wide range of concentrations and exposure times has been reported; however, there is still a paucity of data on the optimum MMC concentration and dose that would be most effective for trabeculectomy without increasing complications significantly.

The Cox proportional hazard analysis was used in our study to identify potential risk factors for surgical failure. Mitomycin C dosing was the strongest predictor of success in the univariable and multivariable analysis. Patients who received MMC 0.4 mg/ml were almost half as likely to experience surgical failure compared to the patients who received MMC 0.2 mg/ml. A randomized clinical trial comparing SIBS microshunt to trabeculectomy[10] revealed the SIBS microshunt to be significantly less effective than trabeculectomy in terms of IOP reduction at 1 year. The lower success in the SIBS microshunt group might be explained by the exclusive use of a lower MMC concentration (0.2 mg/ml). Although the MMC concentration was the same for both groups, the mechanism and location of the bleb of each surgery is different. The microshunt bleb is more posterior, where the midposterior Tenon's capsule is over twice as thick compared to the anterior Tenon's capsule[32] adjacent to the limbus, where trabeculectomy is performed (and tenons isn't always sutured back to its insertion in trabeculectomy whereas it is routinely in microshunt surgery). Furthermore, initial flow conditions (focal vs. diffuse) are different between the microshunt and trabeculectomy. These factors could explain why a lower MMC concentration may achieve an adequate antifibrotic effect

in trabeculectomy, while a higher MMC concentration would be necessary to obtain the same effect in microshunt blebs. Although SIBS has been shown to be highly biocompatible,[12] any implantation of a foreign material could induce additional fibroblast proliferation creating a physical barrier to isolate the material from the rest of the body.[33] Wound healing and scarring are complex processes, and the healing response may not be the same in those 2 procedures, thus requiring different antifibrotic doses.

Although increasing MMC concentration may improve surgical success, this can also increase complications, with previous studies showing an association between a higher dose of MMC and greater complication rates in trabeculectomy.[9,34,35] One of the main challenges of glaucoma filtering surgery is the control of aqueous humor outflow, especially in the early postoperative period, due to the risk of hypotony. In trabeculectomy, the resistance offered by the scleral flap, Tenon's and conjunctiva will dictate the pressure drop and the risks of hypotony-related complications. On the other hand, in SIBS microshunt implantation, the aqueous humor outflow is controlled not only by the resistance of the surrounding tissues but also by the presence of a device designed to prevent hypotony. In this scenario, a higher concentration of MMC could be less prone to cause hypotony-related complications. This rationale could explain why there was no significant difference in hypotony-related adverse events between the groups in our study. Also, no cases of failure occurred due to persistent hypotony in the MMC 0.4 mg/ml group. Similar trends were reported by Armstrong et al[36] where no differences in overall and hypotony-related complications were found in eyes that received different concentrations of MMC in microshunt implantation. In contrast, other SIBS microshunt studies found an association between higher complication rates and MMC doses $>$ 0.2 mg/ml, but most complications were early and self-limiting.[15,16] Some bleb complications may occur years after surgery; thus, a longer follow-up would be ideal to conclude that this high dosage of MMC is safe when it comes to long-term MMC complications.

Most of the baseline characteristics were similar between groups, strengthening the validity of this study. The baseline characteristics that did differ significantly between groups would have been expected to favor higher success rates in the 0.2 mg/ml group, which included older patients, more women, and a higher percentage of white patients. These variables have been postulated to be associated with a higher success rate in bleb surgery due to a reduced risk of fibrosis.[37,38]

Although randomized clinical trials are the gold standard for evaluating causal relationships, this study used a one-stage individual patient data mega-analysis as a powerful statistical technique and high level of evidence for combining the results of multiple clinical studies.[39,40] A one-stage approach was chosen to aggregate individual patient level data, as opposed to a two-stage meta-analytic approach aggregating summary statistics from each trial, because not all included studies reported summary HRs for MMC dose, and access to individual patient level data from all trials was readily available. In a one-stage approach, accounting for differences in baseline hazard function magnitudes between patient clusters (trial, site, eye) using the nested random effects model we employed is critical, given the heterogeneity implicit in combining trials of varying designs. Furthermore, the multitrial, multicenter design, including different countries and sites, facilitates the external generalizability of our results.

However, this study has limitations. We pooled raw data from different studies, with varying study designs. For example, MMC dosing was standardized in some studies and left to the surgeon's discretion in other studies. There was no randomization for the 2 different MMC concentrations, and some sites used only 1 concentration, which can lead to selection bias, yet one would postulate that patients selected for the MMC 0.4 mg/ml group would be at higher risk for failure. In this study, the MMC application exposure time was 2 minutes in most eyes, but in some eyes the duration was 3 minutes. Although this may be a limitation, the number of patients receiving 3 minutes was small. Furthermore, previous studies showed little to no difference in variable exposure times to MMC.[28,30] Although the number of patients in each group was asymmetrical, there was still a large enough sample size in the MMC 0.4 mg/ml group, and both groups had similar baseline characteristics.

In conclusion, this study demonstrated higher success rates with greater IOP reduction in patients who underwent SIBS microshunt implantation with MMC 0.4 mg/ml compared to 0.2 mg/ml. In addition, higher MMC concentration was associated with lower needling and surgical revision rates but was not associated with an increased occurrence of complications. The results of this study support that a higher concentration of MMC should be considered to optimize surgical results when implanting the SIBS microshunt.

Footnotes and Disclosures

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Abbreviations and Acronyms:
CI = confidence interval; **HR** = hazard ratio; **IOP** = intraocular pressure; **IQR** = interquartile range; **MIBS** = microinvasive bleb surgery; **MMC** = mitomycin C; **POAG** = primary open-angle glaucoma; **SIBS** = polystyrene-isobutylene-styrene.

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