BMJ Open Ophthalmology

# Rates of visual field change and functional progression in glaucoma following trabecular microbypass implantation of iStent technologies: a meta-analysis

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**To cite:** Gillmann K, Hornbeak DM. Rates of visual field change and functional progression in glaucoma following trabecular microbypass implantation of iStent technologies: a meta-analysis. *BMJ Open Ophthalmology* 2024;**9**:e001575. doi:10.1136/bmjophth-2023-001575

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjophth-2023-001575).

Received 12 November 2023
Accepted 30 January 2024



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## ABSTRACT

**Background/aim** While intraocular pressure (IOP) remains the only modifiable risk factor for glaucoma progression, the ultimate goal of glaucoma management is to preserve patients' functional vision and quality of life. To this end, minimally invasive glaucoma surgeries (MIGSs) aim to reduce IOP with minimal eye trauma. Commonly used MIGS devices include iStent technologies, which have well-documented IOP-reducing potential and favourable safety profiles. However, no study concluded on their effect on the rates of visual field (VF) changes. The aim of this meta-analysis is to determine the long-term effect of iStent technology implantation on glaucoma functional progression.

**Methods** Electronic medical literature databases were searched to identify studies reporting on iStent technologies. Reports with follow-up durations <12 months, retention rates <75% and missing VF data were excluded. Fifteen studies reporting on 1115 eyes were identified. The overall weighted mean VF mean deviation (MD) progression, IOP reduction and follow-up duration were calculated.

**Results** Weighted mean IOP at baseline was 19.0±3.1 mm Hg. At the end of a 37.9-month mean follow-up (range 12–96 months), a weighted mean 26.6% IOP reduction was achieved (range 15.2%–42.3%). Over the same duration, the weighted mean VF MD progression rate was −0.02±0.34 dBs/year, from a mean baseline of −5.76±5.68 dBs.

**Conclusion** In this review, which examines functional stability of 1115 eyes, iStent technologies achieved a mean rate of progression of −0.024 dBs/year with serial standard automated perimetry, which is similar to that reported in non-glaucomatous eyes and slower than that reported in medically treated glaucoma.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While intraocular pressure (IOP) is an important factor in glaucoma management, several groups have been advising for a shift in the focus of glaucoma clinical trials towards biomarkers that better represent disease stability, such as structural, functional or composite endpoints. iStent technologies have well-documented IOP-reducing potential and favourable safety profiles, but no study concluded on their effect on the rates of functional progression in glaucoma. In the literature, cohorts with treated glaucoma exhibited mean progression rates ranging from −0.22 to −0.67 dBs a year.

### WHAT THIS STUDY ADDS

⇒ In this meta-analysis, which examines functional stability of 1115 eyes, iStent technologies achieved a mean rate of progression of −0.024 dBs a year with serial standard automated perimetry, which is similar to that reported in non-glaucomatous eyes and slower than that reported in treated glaucoma. Interestingly, a weighted mean IOP reduction of 26.6% was sufficient to achieve this functional effect, while large cohort studies reported 3–18 fold higher rates of functional progression despite similar or higher mean IOP reductions.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ While specifically designed and powered trials would be useful to confirm these results, the present findings suggest that early trabecular bypass surgery may be beneficial in stabilising glaucoma progression. Further research is also warranted to ascertain the reasons behind the lack of correlation between functional progression and IOP reduction.

## INTRODUCTION

Glaucoma, a progressive optic neuropathy, is a leading global cause of blindness, with an estimated 15%–20% of patients losing sight in at least one eye within 20 years of diagnosis.[1 2] In response to the escalating burden of the disease, the landscape of its management has experienced a profound transformation over the past decade. Amongst these evolutions, a vast number of relatively safe and effective minimally invasive glaucoma surgery (MIGS) techniques have emerged, bridging the gap between pharmacological treatments and traditional filtering surgery, and providing ophthalmologists with an unprecedented

armamentarium of treatment options.[3 4] However, this abundance of options has led to extensive debates over the choice of these techniques in a context of heterogeneous reports and limited evidence.[5]

To date, intraocular pressure (IOP) remains the only modifiable risk factor for glaucoma progression, and as such, is the cornerstone of nearly all glaucoma treatments. IOP measurements are also readily available, convenient and inexpensive, making them attractive endpoints for glaucoma trials.[6] However, the ultimate goal of glaucoma management is not to lower IOP, but to preserve patients' functional vision and quality of life.[7] While IOP is an important factor in glaucoma management, the World Glaucoma Association consensus group and others have been calling for a shift in the focus of glaucoma clinical trials towards biomarkers that better represent disease stability, such as structural, functional or even composite endpoints, in order to improve decision-making in glaucoma.[8 9]

Commonly used MIGS devices include iStent technologies (Glaukos, Aliso Viejo, California, USA), which are microscale biocompatible microbypass stents designed for ab interno implantation through the trabecular meshwork.[10] There are currently four models of iStent devices on the market: the original iStent (comprising one stent), the iStent inject and iStent inject W (comprising two stents) and the iStent infinite (comprising three stents). All four models rely on the same working principle: reducing IOP by facilitating aqueous outflow from the anterior chamber into Schlemm's canal.[11] iStent technologies, as a minimally invasive surgical intervention, aim to allow patients and clinicians to avoid the limitations of topical medication. Such limitations can include widespread non-adherence, ocular surface disease, local and systemic side effects, costs, caregiving burden, IOP fluctuations, and diminished quality of life. In this way, by intervening earlier in a patient's treatment course, visual function may be better preserved and risk of glaucoma progression may be lessened. Over the years, a robust amount of clinical evidence has been gathered on iStent technologies, much of which focuses on the device's IOP-lowering and medication-lowering potential, coupled with safety outcomes. Across these trials, the reported IOP reduction achieved following iStent implantation ranges from 15.2% to 42.3% depending on the study population and surgical goals, but as far as we are aware, no study concluded on the effect of iStent technologies on the rates of visual field (VF) changes.[12 13]

The aim of this meta-analysis is to determine the long-term effect of iStent technology implantation on glaucoma functional progression through the analysis of VF data from the scientific literature.

## METHODS

The present meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (figure 1).

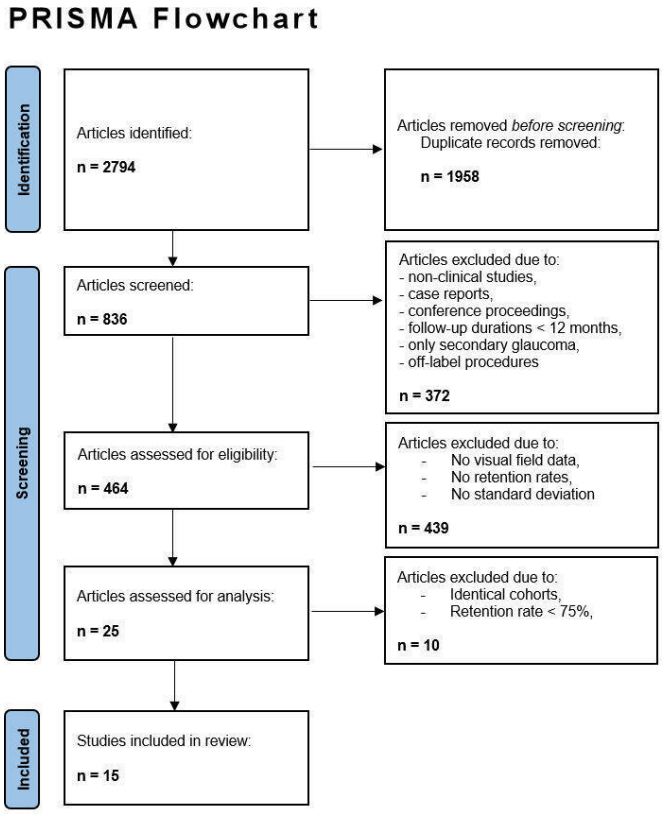


**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart showing the systematic review and screening process.

The keywords "iStent", "microbypass" and "trabecular bypass" were used to search electronic medical literature databases (PubMed, EMBASE, Web of Science, Cochrane Library, Ovid) to identify articles referring to all iStent devices. All identified reports were included in the initial screening before applying the following criteria for exclusion.

Identified articles underwent initial screening through their titles and abstracts, excluding non-clinical studies, case reports, conference proceedings, studies with follow-up durations under 12 months, retention rates below 75%, studies focused solely on secondary glaucoma and reports missing any of the data used in the present analysis. Studies or subgroups of eyes that underwent off-label procedures (including the combination of iStent devices with other glaucoma procedures) were disregarded. Literature review and article screening were carried out independently by two authors (DMH and KG). Any discrepancy was resolved through discussion. Retained articles were carefully read in full to identify and retain only those containing preoperative and postoperative VF mean deviation (MD). When several reports were published based on the same cohort, only the one with the longest duration was considered. Articles reporting on the same preoperative cohort size from the same institution, with the same baseline characteristics, were considered duplicates.

The included articles were quality assessed based on some key aspects laid out in the Cochrane collaboration's tool, including the handling of missing data, incomplete reporting, potential conflicts of interest and risks of bias (figure 2A).[14] The body of evidence was also assessed using the GRADE's definition of quality.[15]

The following data were extracted from the included articles: enrolled eye count, surgical technique (stand-alone or combined with cataract surgery), follow-up duration, baseline and last-reported medicated IOP, anti-glaucoma medication, and VF MD. Data extracted from each individual study are presented in figure 2. Based on these, for each study, the absolute and relative IOP and treatment reductions were calculated as the difference between the mean baseline value and the mean value reported at the considered timepoint. The mean rate of VF MD progression was calculated as the difference in reported MD divided by the follow-up duration and is presented for each individual study in figure 2B. The overall weighted mean VF MD progression, IOP reduction and follow-up duration were subsequently calculated using the weighted arithmetic mean formula: $(\sum^{n}_{i=1} w_i X_i) / (\sum^{n}_{i=1} w_i)$, where x is the value and w is the weight. The weighted mean SD was calculated using the following formula: $\sqrt{((n_1-1)s_1^2 + (n_2-1)s_2^2 + \ldots + (n_k-1)s_k^2 / (n_1+n_2+\ldots+ n_k-k))}$. The Cauchy-Schwarz inequality was used to estimate the SD upper bound, based on the following formula: $\mathrm{Var}(X-Y)=\sigma_x^2/n + \sigma_y^2/ n-2\ \sigma_{xy}$. The effect of heterogeneity was assessed using subgroup analysis when significant differences could be elicited between cohorts, including to estimate the effect of combined cataract surgery on outcome measures. Student's t-test was used for intergroup comparisons. All analyses were performed using a commercially available software (Stata V.17.0, StataCorp).

## REVIEW

The keyword search carried out on 15 March 2023 identified 2794 peer-reviewed articles, with 1958 duplicates excluded. Following preliminary screening, a further 372 articles were excluded. Fifty-seven reports included some VF data, among which 25 reports demonstrated substantial long-term data for analysis. Out of these, eight were successive reports on the same initial cohorts, and a further two reports did not match our retention rates threshold (online supplemental material 1). Ultimately, a total of 15 articles were retained for analysis, with a collective dataset including 1115 eyes.[16–31] Seven of these were prospective studies and two were randomised controlled trials. The PRISMA flow chart is included in figure 1.

No significant risk of bias was identified in the retained articles. Figure 2 reports the risk assessment and characteristics of the 15 studies included in the present analysis. Six of these articles studied the effect of stand-alone iStent implantation, while eight solely focused on procedures combined with cataract surgery, and one study included both stand-alone and combined procedures. All studies analysed the effect of the original iStent microbypass (443 eyes) and the iStent inject devices (603 eyes). No iStent inject W or iStent infinite devices were used in any of the included studies. Based on GRADE guidelines, our overall assessment of certainty in the body of evidence is moderate, meaning that the true effect is likely to be close to the estimate resulting from the present analysis, but that further research particularly in the form of randomised controlled trials, will be required to increase our confidence with these results.

The weighted mean follow-up duration was 37.9 months, ranging from 12 to 96 months. The weighted mean IOP at baseline was 19.0±3.1 mm Hg, achieving a mean 26.6% reduction at the end of the follow-up (range 15.2%–42.3%).

Over the follow-up duration, the weighted mean VF MD decreased from −5.76±5.68 dBs to −5.91±5.82 dBs, at a mean rate of −0.024±0.34 dBs/year. Of the considered studies, 7 (46.7%) reported on average a statistical improvement in VF MD, and 2 (13.3%) reported a mean progression rate in excess of −0.3 dBs/year.

The weighted mean MD progression was −0.01±0.42 dBs/year following combined procedures and −0.07±0.62 dBs/year following stand-alone procedures (p=0.0197). The progression rate did not differ significantly between studies of the original iStent microbypass (−0.03±0.62 dBs/year) and studies of the iStent inject (−0.01±0.43 dBs/year; p=0.482).

## DISCUSSION

In this wide cohort of 1115 eyes treated with iStent devices, the average progression rate was −0.024 dBs per year. If a blind eye is considered to have an MD between −25.0 dBs and −30.0 dBs, it would take a healthy eye over a thousand years to become blind at this rate of progression. While procedures combined with cataract surgery achieved even lower progression rates at a mean of −0.01 dBs per year, stand-alone iStent implantation still resulted in mean progression rates of −0.07 dBs per year, comparing favourably with the documented progression rates for ocular hypertension and medically treated glaucoma (as discussed below).

Limited research studies have examined the progression rate of untreated glaucomatous eyes because of the ethical implications such trials would have. However, the Early Manifest Glaucoma Trial randomised newly diagnosed glaucomatous eyes to either a control group or a medical treatment group. After a mean follow-up of 5.8 years, the mean VF loss rate was −0.67 dB/year across all untreated eyes, with substantial differences between open-angle glaucoma subtypes, ranging from −0.22 dB/year in normal-tension glaucoma, to −0.46 dB/year in primary open-angle glaucoma and −1.13 dB/year in pseudoexfoliation glaucoma.[32] Another triple-masked study conducted by Garway-Heath *et al* compared the effect of topical latanoprost and placebo on VF progression in open-angle glaucoma, and reported a progression rate of −0.29 dB/year in the control group.[33]

A

| Study | Prospective | Randomised | Masked IOP measurement | Blinding of outcomes assessment | Incomplete data outcome | Retention rate (%) | Type of visual field |
|---|---|---|---|---|---|---|---|
| Chang et al. 2017 | yes | | yes | | no | 94.9 | SITA Standard |
| Berdahl et al. 2020 | yes | | | | no | 100.0 | Unspecified |
| Clement et al. 2022 | | | | | n/a | 100.0 | Unspecified |
| Fechtner et al. 2019 | yes | yes | yes | | no | 90.7 | Unspecified |
| Gallardo et al. 2019 (Controlled glaucoma) | | | | | n/a | 100.0 | SITA-Fast |
| Gallardo et al. 2019 (Uncontrolled glaucoma) | | | | | n/a | 100.0 | SITA-Fast |
| Hengerer et al. 2022 (Combined sub-group) | yes | | | | no | 97.5 | Unspecified |
| Hengerer et al. 2022 (Standalone) | yes | | | | no | 95.5 | Unspecified |
| Katz et al. 2018 (2 devices) | yes | yes | | | no | 92.7 | Unspecified |
| Katz et al. 2018 (3 devices) | yes | yes | | | no | 95.0 | Unspecified |
| Lindstrom et al. 2016 | yes | | | | no | 94.7 | SITA Standard |
| Manning et al. 2019 (iStent microbypass) | | | | | n/a | 100.0 | Unspecified |
| Manning et al. 2019 (iStent inject) | | | | | n/a | 100.0 | Unspecified |
| Nitta et al. 2020 | | | | | n/a | 98.1 | Unspecified |
| Saheb et al. 2020 | yes | | yes | | no | 76.9 | SITA Standard |
| Salby and Skalicky 2020 | | | | | n/a | 100.0 | Unspecified |
| Salimi et al. 2020 | | | | | n/a | 100.0 | Unspecified |
| Salimi et al. 2021 | | | | | n/a | 98.3 | Unspecified |
| Salimi and Harasym 2021 | | | | | n/a | 100.0 | Unspecified |

B

| Study | Device implanted | Number of devices | Procedure | Type of glaucoma | Country | Mean baseline visual field MD (dBs) | SD | Number of eyes | Follow-up duration (months) | Mean rate of MD change (dBs / year) |
|---|---|---|---|---|---|---|---|---|---|---|
| Chang et al. 2017 | original | 2 | Standalone | OAG | Armenia | -6.47 | 6.9 | 37 | 36 | 0.42 |
| Berdahl et al. 2020 | inject | 2 | Standalone | OAG | Armenia | -5.6 | 5.4 | 53 | 48 | 0.05 |
| Clement et al. 2022 | inject | 2 | Combined | OAG, PAC, OHT | Australia | -5.09 | 5.62 | 180 | 36 | -0.02 |
| Fechtner et al. 2019 | original | 2 | Standalone | OAG | Armenia | -7.5 | 8.8 | 49 | 60 | -0.06 |
| Gallardo et al. 2019 (Controlled glaucoma) | original | 1 | Combined | POAG | USA | -9.2 | 8.3 | 43 | 36 | 0.30 |
| Gallardo et al. 2019 (Uncontrolled glaucoma) | original | 1 | Combined | POAG | USA | -8.08 | 6.72 | 32 | 36 | -0.02 |
| Hengerer et al. 2022 (Combined sub-group) | inject | 2 | Combined | OAG | Germany | -6.6 | 2.8 | 79 | 60 | -0.02 |
| Hengerer et al. 2022 (Standalone) | inject | 2 | Standalone | OAG | Germany | -7 | 3.5 | 42 | 60 | -0.02 |
| Katz et al. 2018 (2 devices) | original | 2 | Standalone | OAG | Armenia | -5.2 | 5.65 | 38 | 42 | -0.55 |
| Katz et al. 2018 (3 devices) | original | 3 | Standalone | OAG | Armenia | -4.81 | 4.22 | 38 | 42 | -0.60 |
| Lindstrom et al. 2016 | inject | 2 | Standalone | OAG | Armenia | -4.9 | 5.3 | 54 | 48 | -0.02 |
| Manning et al. 2019 (iStent microbypass) | original | 1 | Combined | OAG, PAC, OHT | Australia | -4.89 | 5.5 | 67 | 12 | 0.14 |
| Manning et al. 2019 (iStent inject) | inject | 2 | Combined | OAG, PAC, OHT | Australia | -4.35 | 7.4 | 70 | 12 | -0.07 |
| Nitta et al. 2020 | original | 1 | Combined | OAG | Japan | -8.1 | 4.6 | 52 | 24 | 0.10 |
| Saheb et al. 2020 | original | 2 | Standalone | OAG | Armenia | -4.47 | 2.11 | 30 | 60 | 0.16 |
| Salby and Skalicky 2020 | inject | 2 | Combined | POAG | Australia | -3.6 | 3.9 | 63 | 24 | 0.40 |
| Salimi et al. 2020 | inject | 2 | Combined | NTG | Canada | -5.62 | 5.16 | 62 | 12 | -0.35 |
| Salimi et al. 2021 | original | 2 | Combined | POAG | Canada | -5.9 | 6.6 | 57 | 96 | -0.26 |
| Salimi and Harasym 2021 | Either | 2 | Combined | PACG | Canada | -5.7 | 5.5 | 69 | 12 | -0.10 |

**Figure 2** Summary table of the key design (A, top) and clinical characteristics (B, bottom) of all included study. Quality assessment includes whether the study was prospective, randomised, with masked intraocular pressure (IOP) measurements, whether any blinding method was used, or if any incomplete reporting was observed. The retention rate, type of visual field strategy used, type of device studies (original iStent microbypass or iStent inject), the number of devices implanted, whether the procedure was stand-alone or combined with cataract surgery, the type of glaucoma studied (open-angle glaucoma (OAG), primary open-angle glaucoma (POAG), primary angle-closure (PAC), ocular hypertension (OHT) or normal-tension glaucoma (NTG)), the main country in which the studies were conducted, the mean baseline visual field mean deviation (MD) and its SD, the number of eyes involved at baseline, the follow-up duration, and the mean rate of visual field MD progression were also reported for each study.

Substantially more data are available on the rate of VF progression in treated glaucoma, although the types of treatments included in these studies vary widely. A Swedish retrospective review involving 583 eyes with either primary open-angle glaucoma or pseudoexfoliation glaucoma and a mean baseline MD of −10.0 dBs reported a mean progression rate of −0.80 dB/year over a mean 7.8-year follow-up.[34] Notably, a subset of patients (5.6% of the cohort) exhibited a rate worse than −2.5 dB/year. Similarly, a French multicentre study involving 441 eyes over a mean 8.4-year follow-up identified a progression rate of −0.32 dB/year in early primary open-angle glaucoma and −0.54 dB/year in advanced disease.[35] Among non-glaucomatous eyes with ocular hypertension, the mean progression rate was −0.09 dB/year. Another study based on 2208 primary open-angle glaucoma and ocular hypertension patients from the Portsmouth VF database reported a mean progression rate of −0.27 dB/year for the whole cohort over a median 6.7-year follow-up.[36] Over the same period of time, non-glaucomatous eyes with ocular hypertension exhibited a mean progression of −0.06 dB/year. The median baseline MD was −2.0 dBs for best eyes and −3.2 dBs for worst eyes. These rates of progression were similar to that reported within patients from the New York Glaucoma Progression Study and the Japanese Archive of Multicentral Databases in Glaucoma, with respective rates of progressions of −0.28 dB/year and −0.26 dB/year, among large cohorts of predominantly treated primary open-angle glaucoma eyes.[37 38] When considering surgically managed glaucoma, the analysis of 80 eyes having undergone trabeculectomy at Moorfields Eye Hospital showed a mean progression rate of −0.33 dB/year over the first 3.1 postoperative years.[39] Figure 3 presents the observed VF MD progression rates following iStent implantation in comparison to that reported for ocular hypertension and treated glaucoma.

Interestingly, the mean IOP reduction achieved with treatment in the primary open-angle glaucoma cohort considered by Aptel *et al* was greater than 28%, achieved through a combination of pharmacological therapies (in 75.5% of eyes) and of filtering surgery.[35] In the present review, the weighted mean IOP reduction from iStent implantation was slightly less, at 26.6%. Yet, this resulted in 3–18 fold lower mean progression rates. This lack of correlation was also observed in the 6 year outcomes of the Laser in Glaucoma and Ocular Hypertension trial, in which the selective laser trabeculoplasty arm had lower rates of VF progression than the medically treated arm, despite having slightly higher IOP.[40] A number of explanations have been put forward by various authors, including the fact that, within physiological values, IOP does not appear to be directly correlated with functional progression in early glaucoma.[41] In addition, static IOP endpoint rarely take into account other factors responsible for glaucoma progression such as endogenous and exogenous diurnal IOP fluctuations, patient compliance, or non-pressure dependent mechanisms. Although IOP is a key risk factor for glaucoma progression, and the sole modifiable one to date, longitudinal studies have demonstrated that static IOP is not the only pressure-related factor that influences glaucoma progression. Maximum or peak IOP, the range of IOP fluctuations, and its SD all correlate with higher progression rates.[42–44] Moreover, the efficacy of pharmacological treatments is highly dependent on patient adherence which, in the case of glaucoma much like other chronic diseases, tend to be poor.[45] A study confirmed this by comparing VF and pharmacy data within a large cohort of open-angle

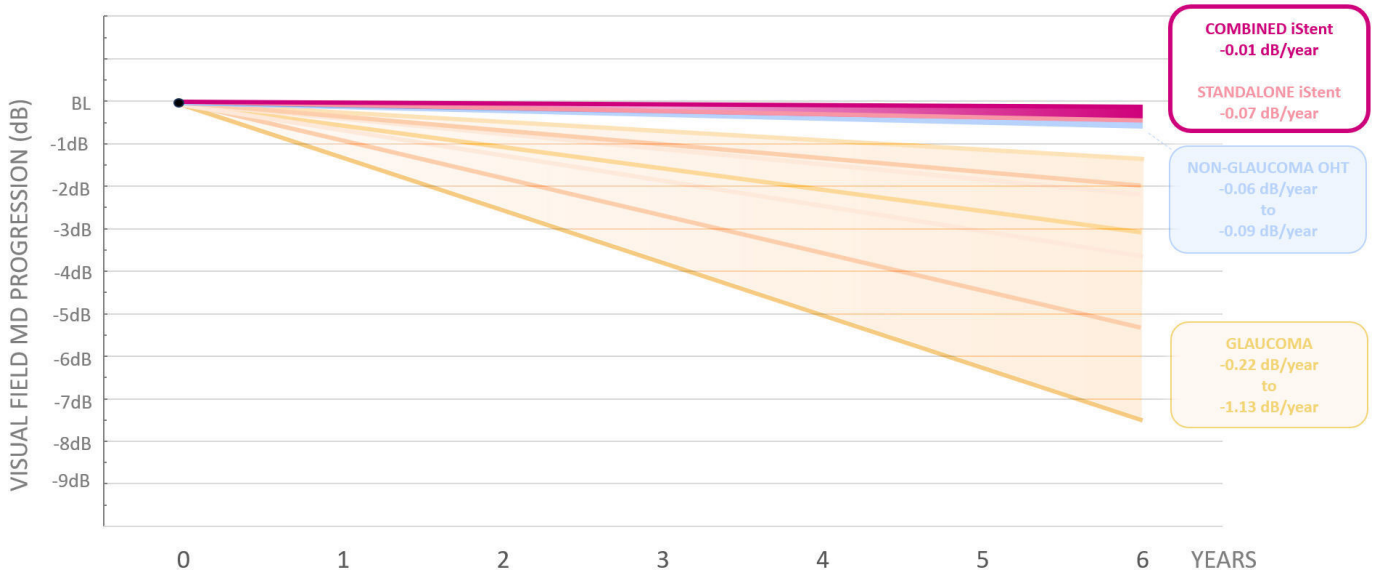


**Figure 3** Observed visual field mean deviation (MD) progression following stand-alone and combined iStent technologies implantation (pink lines) compared with the rates of progression reported in the literature for ocular hypertension (OHT; blue lines) and treated glaucoma (yellow lines). BL, baseline.

glaucoma patients, identifying poor compliance as a direct risk for functional progression.[46] Several authors have also suggested that glaucoma surgery may contribute to normalising IOP-related fluctuations more efficiently and sustainably than pharmacological therapies.[47] The normalisation of IOP fluctuations and the minimisation of patient compliance issues are two potential factors behind why functional progression appears to be slower following iStent implantation than what may be expected from the magnitude of IOP reduction alone. This observation may further support the concept that early surgical intervention in glaucoma may be beneficial in preserving visual function while minimising the effects of long-term topical therapies on quality of life, ocular surface or conjunctival health.[48–51]

Disease severity may also have a role to play in its rates of progression.[52 53] While reports on severity-progression correlations are conflicting,[54] Rao *et al* identified an annual progression increase of 0.02% for each lost dB at baseline in a study of 512 eyes.[55] Aptel *et al* also observed faster progression rates in moderate and advanced glaucoma compared with early glaucoma.[35] However, severe glaucoma showed slower rates, which may be explained by the greater proportion of eyes undergoing surgery and aggressive medical therapy in this subgroup.

The present analysis has a number of limitations. First, data available in the reviewed articles did not permit the comparison of progression rates following iStent implantation in different severities of glaucoma, so more research will be needed to ascertain this. Second, although VF is a straightforward test, it can be prone to biases, notably due to its intertest variability, sensitivity issues or the impact of factors like concomitant cataract.[56 57] This is particularly true as little information was available from the reviewed articles concerning how the MD score was obtained, the test strategy used, the reliability indices, and whether the reported score resulted from the averaging of several values or from a single test. These drawbacks, however, may have a less impact on large heterogenous multistudy pooled cohorts such as the one considered in the present review, as the large number of eyes included should mitigate the impact of variability biases. Additionally, not all VFV progression can be attributed to glaucoma. Other causes like ctaract, age-related macular degeneration, retinal vein occlusion, or neurological diseases such as strokes will gain importance with longer follow-ups and ageing cohorts. It was highlighted that VF MD is affected negatively by lens opacities and positively by removal of cataract. The latter was notably reported to have increased MD by 1.6 dB in the literature.[58] It should be noted that 69.4% of the eyes included in the present analysis underwent cataract surgery at the time of iStent implantation. While this effect may have had a positive bias on the observed progression rates, the observed rates still remained below that reported in the literature for treated glaucoma even when only stand-alone procedures were considered (−0.07 dB/year). In addition, as follow-up durations were relatively long in the considered studies, the development of posterior capsule opacification following combined procedures or the age-related progression of cataract following stand-alone iStent implantation could have caused a gradual reduction in MD which might have cancelled the positive bias of cataract surgery. Moreover, cataract surgery was suggested to increase the rate of MD progression in glaucomatous eyes without prior filtering surgery, with a reported mean postoperative rate of progression of −0.42 dB/year.[59] This negative effect of cataract surgery would be expected to become noticeable over long follow-up periods such as the ones considered in this analysis, suggesting that trabecular bypass may have a protective effect similar to that of trabeculectomy. Furthermore, rapidly progressing conditions such as exudative age-related macular degeneration or vascular diseases may have a dramatic effect on MD values at any one visit, leading to an overestimation of glaucoma progression. An additional cause for bias in reviews of glaucoma trials may be the handling of missing data in included studies. Indeed, most studies on VF have identified small subgroups of fast-progressing eyes. It is likely that some of these would have been present in the considered studies and underwent reoperation, leading to their exclusion from further VF testing and thus from analysis. While this may result in an underestimation of progression rates, the authors of the present analysis have set a low threshold for exclusion of trials with missing data in order to mitigate this risk.

Despite these limitations, the present review analyses data from a large number of eyes followed up in different settings and across different continents, and while it faces some inevitable biases, it attempts to bridge important knowledge gaps. Indeed, existing information remains limited regarding the long-term impact of MIGS on functional outcomes such as VF progression as opposed to solely IOP control. By analysing the existing evidence base, the present report extracts substantive information while also highlighting the need for specifically designed and powered trials to investigate correlations or discrepancies between IOP and functional outcomes. From a broad perspective, long-term clinical trials may benefit from adopting more functional endpoints in glaucoma. Indeed, the present results support the idea that, while an important measurement, IOP may not be the most suitable surrogate endpoint for functional stability.[9] As evidence accrues showing that barometric insult is only a small piece of the much more complex pathophysiology of glaucoma, functional and structural endpoints emphasising the broader picture may lead to new, more clinically relevant conclusions.[60]

In conclusion, iStent technologies have well-documented IOP-reducing potential and favourable safety profiles. In this review, which examines functional stability of 1115 eyes, these devices achieved a mean rate of progression of −0.024 dBs a year with serial standard automated perimetry, which is similar to that reported in non-glaucomatous eyes and slower than that reported in medically treated glaucoma. While specifically designed

and powered trials would be useful to confirm these results, the present findings suggest that early trabecular bypass surgery may be beneficial in stabilising glaucoma progression.

**Contributors** Both authors contributed to the original concept, performed the literature search and review, discussed the results, and contributed to the final manuscript, with KG as guarantor.

**Funding** KG received honoraria from Glaukos for conducting the present study, and DMH is an employee of Glaukos.

**Competing interests** KG received honoraria from Glaukos for conducting the present study. DMH is an employee of Glaukos.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request. The present meta-analysis was not registered. All data used in the present analysis were extracted from publicly available reports. A summary of the extracted data is reported in figure 2.

**Author note** The present meta-analysis adheres to the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA checklist was uploaded as part of this publication and the PRISMA flow chart is included as figure 1.



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