Cost-utility Analysis of Trabecular Micro-bypass Stents (TBS) in Patients With Mild-to-moderate Open-angle Glaucoma in Italy

Antonio Maria Fea
  Department of Surgical Sciences, University of Turin, Turin

Francesco Cattel
  Department of Medical Sciences, University of Turin, Amedeo di Savoia Hospital; City of Science and Health Molinette, Hospital Pharmacy, Turin

Stefano Gandolfi
  Ophthalmology Unit, Department of Biological, Biotechnological and Translational Sciences, University of Parma, Parma

Giorgio Buseghin
  Glaukos, San Clemente, California

Gianluca Furneri (✉ gianluca.furneri@ebmaconsulting.com)
  EBMA Consulting SRL, Melegnano, Milan

Ciro Costagliola
  Department of Medicine & Health Sciences "V. Tiberio", University of Molise, Campobasso

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Research Article

Abstract

Background

Glaucoma is a disease characterized by progressive damage of the optic nerve. Several therapeutic options are available to lower intraocular pressure (IOP). In primary open-angle glaucoma (POAG) patients with inadequate IOP control (or controlled with multiple medical therapies or for whom medical therapy is contraindicated), the implantation of micro-invasive glaucoma surgery devices (MIGS) and concomitant cataract surgery has proved to be more effective in reducing intraocular pressure (IOP), as compared to cataract surgery alone. The objective of this study is to assess the cost-effectiveness of iStent *inject*® device with concurrent cataract surgery vs. cataract surgery alone, in patients with mild-to-moderate POAG, adopting the Italian National Health Service (NHS) perspective.

Methods

Simulation of outcomes and costs was undertaken using a Markov model with 4 health states and one-month cycles, that is used to simulate the prognosis of these patients. Efficacy data were obtained from the randomized clinical trial (RCT). A lifetime horizon was adopted in the analysis. A discount rate of 3.5% was applied to both costs and effects. The Italian National Healthcare Service (NHS) perspective was considered, therefore only healthcare direct costs (acquisition of main interventions and subsequent procedures; medications; monitoring and follow-up; adverse events). Model robustness was tested through sensitivity analyses.

Results

Results of the base-case analysis showed that the total lifetime costs were higher in the iStent inject® + concurrent cataract surgery, compared with the cataract surgery alone group (€8,368.51 vs. €7,134.71 respectively). iStent inject® + concurrent cataract surgery was cost-effective vs. cataract surgery alone, with an incremental cost-effectiveness ratio of €13,037.01 per quality-adjusted life year (QALY) gained. Both one-way deterministic and probabilistic sensitivity analyses confirmed robustness of base-case results. The acceptability curve of cost-effectiveness (CEAC) analysis showed that iStent inject® + cataract surgery would have a 98% probability of being cost-effective, compared to cataract surgery alone, when the willingness to pay (WTP) is equal to €50,000 per QALY gained.

Conclusions

The results of the cost-utility analysis confirm that iStent inject® + cataract surgery is a cost-effective option for the treatment of patients affected by mild-to-moderate POAG, compared with cataract surgery alone, when evaluated from the Italian NHS perspective.

Trial registration: Not applicable

Background

Glaucoma is a disease characterized by progressive damage of the optic nerve [1] and is the second cause of blindness globally, after cataract [1]: it affects approximately 66.8 million people worldwide [2,3]. Recent estimates show that about 1 million subjects suffering from glaucoma in Italy; only half of them have a confirmed diagnosis [1]. Every year, about 4,500 new cases of blindness are registered in Italy, and approximately 200,000 blindness cases in total are correlated to this pathology [4].

Primary open-angle glaucoma (POAG) is the most common form of glaucoma, accounting for about 90% of all glaucoma cases [5]. Patients with mild-to-moderate POAG may have significant visual disability, with impairment of their visual field, contrast sensitivity, and light-to-dark and dark-to-light adaptation.

Intraocular pressure (IOP) is the only modifiable risk factor for glaucoma. An abnormality in the trabecular meshwork is the primary cause of reduced aqueous outflow, and therefore of increased IOP. Several therapeutic options are available to lower IOP, including medical therapy, laser trabeculoplasty (ALT/SLT), non-filtering micro-invasive glaucoma surgery (MIGS), anterior filtering surgeries, posterior filtering surgeries [6]. The choice of the optimal therapeutic intervention generally depends on several factors: the IOP level to be targeted, the entity of the anatomical eye damage induced by POAG, the disease progression rate, age and presence of comorbidities, level of ocular inflammation. Cataract and glaucoma frequently occur in the same patient, and their concomitant presence increases with age [7,8].

In patients with medically controlled, non-severe glaucoma and cataract, small-incision cataract extraction (phacoemulsification) alone may be a valid option to reduce IOP and to control glaucoma progression [9,10]. However, in a relevant number of POAG cases (patients with inadequate IOP control; patients controlled with multiple medical therapy; patients for whom medical therapy is contraindicated), phacoemulsification alone could be insufficient to control POAG progression adequately.

In these subjects, the implantation of micro-invasive glaucoma surgery devices (MIGS) and concomitant cataract surgery has proved to be more effective in reducing intraocular pressure (IOP), as compared to cataract surgery alone [11]. The IOP lowering of simple cataract extraction may also be limited in time [12], whereas combining MIGS with cataract seems to have a more prolonged effect [5,13].

Among MIGS, the trabecular bypass stent (TBS) seems to have an optimal risk-benefit profile in patients with mild-to-moderate POAG.

The iStent *inject*® (Glaukos Corp., San Clemente, CA) TBS device is inserted into the trabecular meshwork through a single corneal entry to improve physiologic aqueous outflow. iStent *inject*® has been shown to lower IOP while reducing ocular hypotensive medication usage in prior studies comparing eyes randomly assigned to cataract surgery and iStent implantation or cataract surgery alone with follow-up through 12 months, up to 48 months [14–17]. While many studies have demonstrated the efficacy of MIGS, there is limited knowledge about the economic implications of MIGS implantation, in patients with POAG, in need of cataract surgery. The objective of this study is to assess the cost-effectiveness of iStent *inject*® device with concurrent cataract surgery vs. cataract surgery alone, in patients with mild-to-moderate POAG, adopting the Italian National Health Service (NHS) perspective.

Method
Model design

The present cost-effectiveness analysis compares the costs and clinical outcomes of iStent *inject*®, in conjunction with cataract surgery, vs. cataract surgery alone, in a single eye of patients with POAG over a lifetime horizon. A Markov model with 4 health states (Figure 1) and one-month cycles, was used to simulate the prognosis of these patients. The model estimated the clinical benefits (in terms of quality-adjusted life years, QALY) and costs associated with the two different alternatives.

The model is based on the assumption that both quality of life outcomes and disease management costs of a hypothetical POAG patient would depend on the severity of the disease, defined according to the Hodapp-Parrish-Anderson scale [18]: i) mild: from 0 to -6 dB; ii) moderate: from -6.01 to -12 dB; iii) advanced: -12.01 to -20 dB; iv) severe / blindness:> -20 dB.

At model start, patients are allocated in one of the four health states. The probabilities of transitioning from one health state to the next (e.g. mild to moderate, moderate to advanced, etc.) are based on the following parameters: i) natural rate of progression of glaucoma (dB) in untreated patients; ii) treatment-attributable delay of disease progression, driven by IOP reduction, determined with the decline of the visual field (VF) defect. Transitions towards more severe health states determine an increase of resource consumption (more frequent consultations and tests) and a progressive reduction of patients' utilities.

The VF deterioration associated with the progression of glaucoma is irreversible; in the model, health state transitions would occur only to states of greater severity.

In the model, patients with inadequate control of VF would require subsequent treatment, which is trabeculectomy. The risk of switching to trabeculectomy is expressed as a time-dependant function, whose shape depends on the IOP-modifying effect of first-line treatment (basically, the larger the IOP reduction the lower the proportion of patients who would need trabeculectomy).

Furthermore, patients can move to the health state "death" at any time, from any of the other health states.

A lifetime horizon was adopted in the analysis. A discount rate of 3.5% was applied to both costs and effects. The Italian NHS (National Healthcare Service) payer perspective was adopted, i.e. considering only direct healthcare resources reimbursed and funded by the NHS.

Clinical inputs

Characteristics of patients at baseline

At model start, patient population (POAG patients in need of cataract surgery) was aged 64.7 years [19]. Consistently with main treatment guidelines and common opinions on MIGS place in therapy, it was assumed that patients receiving iStent inject® had mild-to-moderate glaucoma (50.0% of patients with mild POAG, 50.0% of patients with moderate POAG [20].

Treatment effectiveness

In the model, effectiveness of the two treatment arms depends on two factors: i) IOP reduction obtained with surgical treatment (iStent inject® + cataract surgery vs. cataract surgery alone); ii) IOP reduction obtained with concomitant medical treatment.

Table 1 shows IOP levels and IOP reduction over time for the two alternatives. IOP data at one and two years after surgery were obtained from the randomized clinical trial (RCT) conducted by Samuelson et al 2019 [14]. Since efficacy of treatments is expected to decrease overtime, a 6.7% reduction of clinical effectiveness per year was hypothesized in both treatment arms (based on the estimates provided by the panel of experts) [20], to evaluate the efficacy of the interventions over the time horizon.

Table 1. Efficacy inputs with medication discontinuation at 8.6 months [Source: elaborated from Samuelson et al 2019 [14]].

Time (years)	iStent + Cataract surgery		Cataract surgery	
	IOP (mmHg)	IOP reduction (mmHg)*	IOP (mmHg)	IOP reduction (mmHg)*
0	24.8**	-	24.5**	-
1	17.7	7.1**	19.0	5.5**
2	18.3	6.6**	20.1	4.4**
3	19.1	5.7	20.9	3.6
4	19.4	5.4	21.2	3.3
5	19.7	5.1	21.3	3.2
6	20.0	4.8	21.5	3.0
7	20.3	4.5	21.7	2.8
8	20.5	4.3	21.8	2.7
9	20.8	4.0	22.0	2.5
10	21.0	3.8	22.1	2.4
10+	21.2	3.6	22.2	2.3

IOP=intraocular pressure.

*Intraocular pressure reduction vs. baseline.

**IOP and IOP reduction data, at one and two years, were obtained from the randomized clinical trial (RCT) conducted by Samuelson et al 2019 [14] and adjusted for the time-to-discontinuation. Baseline IOP: 24.8±3.3 mmHg vs. 24.5±3.1 mmHg in the iStent + Cataract surgery vs. Cataract surgery groups, respectively (P = 0.33).

Beyond surgical treatment, IOP can be also reduced with concomitant medical therapy. Treatment effectiveness depends on the number of medications used. The progressive reduction of medication use was modelled, for the two alternatives, by incorporating the discontinuation rate of medical therapy [21]. The weighted average time-to-discontinuation was 8.6 months, according to Nordstrom et al. 2005 [22]. It was also assumed that the IOP increase due to discontinuation was equal to the difference in baseline medicated versus unmedicated IOP (7 mmHg), derived from Samuelson et al. 2011 [23].

As mentioned earlier, IOP reduction has the effect of reducing the risk of VF decline, measured with the Hodapp-Parrish-Anderson scale. If glaucoma were untreated, VF monthly decline would be -0.0508 dB [24]. Instead, if treated, one-unit reduction in IOP (mmHg) would determine a 9.5% decrease of the VF decline, according to the Early Manifest Glaucoma Trial (EMGT) [24]. These assumptions were used to determine transition probabilities between mild and moderate, moderate and advanced, advanced and severe health states will depend on IOP reduction.

Furthermore, IOP reduction has the effect of reducing the risk of VF disease progression, which is used in the model to estimate the proportion of patients who would need to receive trabeculectomy. The natural disease progression of glaucoma patients is described by Heijl et al. [24] and can be assimilated to a lognormal distribution. From published literature it was observed that one-unit reduction in IOP (expressed in mmHg) was associated with a 12% reduction of the risk of disease progression, compared with the natural history of the disease (hazard ratio: 0.88; Leske et al. 2003 [25]).

Efficacy of subsequent treatments

In the model, it was assumed that patients experiencing disease progression received subsequent treatment. According to Italian expert opinion, the most plausible treatment following cataract surgery (with or without MIGS implantation) was trabeculectomy. Efficacy data for trabeculectomy, expressed in terms of IOP reduction, were obtained from an indirect comparison analysis conducted by the National Institute of Health Care and Excellence (NICE) [26]. According to this source, trabeculectomy reduced IOP of 6.48 mmHg.

Mortality

At any time and health state, patients could move to the death health state. However, it was assumed that glaucoma would not modify (i.e. increase) the risk of death. For this reason, mortality probabilities have been obtained from the general mortality tables of the Italian population (source: Italian Institute of Statistics, ISTAT; year 2017 [27]).

Cost inputs

To provide a thorough assessment of the economic impact of glaucoma management, the following costs were included in the analysis: i) costs associated with main interventions; ii) costs of subsequent procedures; iii) costs of medications; iv) costs of monitoring and follow-up; v) costs of adverse events.

Table 2 lists all cost input data and resource consumption assumptions used in the model.

The cost of cataract surgery was derived from the national tariff of hospital procedures [28].

Some outpatient procedures are available within several regional health systems and carried out in regional health structures with recognized clinical validity but are not present in the national nomenclator.

For this reason, the costs of certain procedures have been obtained from the regional tariff nomenclators.

The cost associated with iStent inject + cataract surgery was calculated based on Glaukos market data and the average costs of procedures in Tuscany, Umbria and Veneto regions [29–31].

The cost of trabeculectomy was calculated as the average tariff of interventions ("Trabeculectomy ab externo") in Friuli Venezia-Giulia, Molise and Veneto regions [30,32,33]).

Acquisition costs of glaucoma medical therapy were included in the analysis. Monthly costs of the different medical therapies used in glaucoma were calculated using the ex-factory price (branded or generic) [34,35]. Then, these costs were multiplied by the respective market shares of these therapies in Italy [36], and finally summed up to determine an average monthly cost of glaucoma medical therapy in Italy.

The costs of glaucoma disease monitoring were included in the model; it was assumed that resource consumption depended on disease severity [20]. The following resources were considered: i) ophthalmologist consultation; ii) gonioscopy; iii) visual field test; iv) optic disc imaging. Finally, the costs for the management of treatment-related adverse events were calculated by multiplying the unit costs in the Italian practice [28,37], by the respective adverse event rates [38]. Only adverse events with at least 3% difference between the two treatment arms were included. The adverse event costs were one-time costs, applied only at the beginning of the simulation, corresponding with the index intervention.

Table 2. Cost input included in the analysis.

Type	Description	Value	Source
Main procedures	Glaucoma + cataract surgery cost (€)	€2,294.20	iStent acquisition cost + procedures cost [29−31,39]
	Cataract surgery cost (€)	€994.00	DH 39 [28]
Subsequent procedures	Trabeculectomy cost (€)	€1,969.10	Code 12.64 [30,32,33]
Medications	Bimatoprost cost (€)	€20.23	Generic ex-factory price [34]
	Bimatoprost + timolol cost (€)	€27.25	Branded ex-factory price [35]
	Brinzolamide + timolol cost (€)	€16.88	Branded ex-factory price [35]
	Dorzolamide + timolol cost (€)	€7.33	Generic ex-factory price [34]
	Travoprost + timolol cost (€)	€18.26	Generic ex-factory price [34]
	Timolol cost (€)	€5.70	Generic ex-factory price [34]
	Tafluprost cost (€)	€25.94	Branded ex-factory price [35]
	Bimatoprost MS (%)	15.6%	[36]
	Bimatoprost + timolol MS (%)	11.5%	
	Brinzolamide + timolol MS (%)	13.9%	
	Dorzolamide + timolol MS (%)	16.4%	
	Travoprost + timolol MS (%)	6.6%	
	Timolol MS (%)	25.4%	
	Tafluprost MS (%)	10.7%	
Disease monitoring	Ophthalmologist consultation cost (€)	€20.66	Code 95.02 [37]
	Gonioscopy cost (€)	€7.75	Code 95.26 [37]
	VF defect test cost (€)	€16.78	Code 95.05 [37]
	Optic disc imaging cost (€)	€90.00	Code: 95.17 [31]
	Incidence ophthalmologist consultation (n/month), mild glaucoma	0.17	[20]
	Incidence ophthalmologist consultation (n/month), moderate glaucoma	0.25	
	Incidence ophthalmologist consultation (n/month), advanced glaucoma	0.33	
	Incidence ophthalmologist consultation (n/month), severe/blind glaucoma	0.25	
	Incidence gonioscopy (n/month), mild glaucoma	0.08	
	Incidence gonioscopy (n/month), moderate glaucoma	0.08	
	Incidence gonioscopy (n/month), advanced glaucoma	0.08	
	Incidence gonioscopy (n/month), severe/blind glaucoma	0.08	

	Incidence VF defect test (n/month), mild glaucoma	0.17	
	Incidence VF defect test (n/month), moderate glaucoma	0.17	
	Incidence VF defect test (n/month), advanced glaucoma	0.25	
	Incidence VF defect test (n/month), severe/blind glaucoma	0.17	
	Incidence optic disc imaging (n/month), mild glaucoma	0.17	
	Incidence optic disc imaging (n/month), moderate glaucoma	0.17	
	Incidence optic disc imaging (n/month), advanced glaucoma	0.33	
	Incidence optic disc imaging (n/month), severe/blind glaucoma	0.17	
Adverse events	Hyperaemia unit cost (€)	€20.66	Code 89.07 [37]
	Stent obstruction unit cost (€)	€1,522.00	DH 42 [28]
	Incidence hyperaemia, iStent + cataract group (%)	0.8%	[38]
	Incidence stent obstruction, iStent + cataract group (%)	6.2%	
	Incidence hyperaemia, cataract surgery only group (%)	5.9%	
	Incidence stent obstruction, cataract surgery only group (%)	0.0%	

DH=day hospital; MS=market share; VF=visual field.

Utility inputs

Quality-adjusted life years (QALYs) were estimated as the sum of the life years spent in each health state, weighted by the associated utilities, thus reflecting the average health-related quality of life (HRQOL) of glaucoma patients in each stage of the disease.

Table 3 shows the utilities associated with the health states of the model. These values have been extracted from two studies conducted in 2010 and 2012 in the Netherlands [40,41], which correlated the loss of vision with health-related quality of life (HRQoL).

Table 3. Utilities associated with the health states of the model [40,41].

Health state	Utility
Mild glaucoma	0.847
Moderate glaucoma	0.781
Advanced glaucoma	0.704
Severe/blind glaucoma	0.594

Disutility for trabeculectomy was estimated from the same study conducted by Van Gestel et al. [41] (Table 4). Disutilities for medication-related adverse events were subtracted to the health state utilities. Such disutility values were multiplied by the probability of experiencing the adverse event, to obtain an average disutility value. Also, since not all patients were receiving medications at each Markov cycle, the disutility value was weighted by the proportion of patients receiving therapy at each Markov cycle. The incidence rates of adverse events in patients receiving prostaglandins, beta-blockers and carbonic anhydrase inhibitors were 8%, 8%, and 14%, respectively [42]; market shares of these drugs were 35.2%, 15.2%, and 49.6%, respectively (obtained from the market shares of the single drugs reported in the Table 2). Consequently, the medication weighted incidence of adverse events was 8.9%; the corresponding disutility value was calculated multiplying this percentage by the disutility value for medication-related averse events (Table 4), estimated from the Van Gestel et al. study [41].

Table 4. Disutilities included in the model [41].

Description	Disutility	CI (95%)	Source
Trabeculectomy	-0.007	0.005-0.009	[41]
Medication-related AEs	-0.101	0.076-0.126	

AEs=adverse events; CI=confidence interval.

Sensitivity analysis

Deterministic (one-way) and probabilistic sensitivity analyses were carried out to identify the input values with the largest effect on incremental cost-effectiveness ratio (ICER).

For the deterministic sensitivity analysis, the baseline value of each parameter was modified to the upper and lower limits of its 95% confidence interval (95% CI). If the CI was not available, a variation of ± 10% from the baseline value was used.

A probabilistic sensitivity analysis was performed, simultaneously and randomly varying the values of all model parameters (1,000 replications). For the probabilistic analysis, the following probability distributions were used: beta for probabilities and utilities; gamma for costs; normal for efficacy data.

Results

Base-case analysis

Results of the base-case analysis are shown in Table 5. iStent *inject*® + concurrent cataract surgery was more effective than cataract surgery alone, in terms of quality-of-life-adjusted survival (11.11 QALYs, compared with 11.02 QALYs respectively).

The total lifetime costs were higher in the iStent *inject*® + concurrent cataract surgery, compared with the cataract surgery alone group (€8,368.51 vs. €7,134.71 respectively). The higher procedural cost and the acquisition costs of iStent *inject*® were the driver of this cost increase.

Results of the analysis showed that iStent *inject*® + concurrent cataract surgery was cost-effective vs. cataract surgery alone, with an incremental cost-effectiveness ratio of €13,037.01 per QALY gained.

Table 5. Results of Cost utility analysis: base-case.

Treatment	iStent *inject*® + cataract surgery	Cataract surgery
Costs (€)		
Procedures (€)	€ 3,557.00	€ 2,317.06
Medications (€)	€25.59	€51.17
Progression-related (€)	€4,691.45	€4,765.25
Adverse events (€)	€94.46	€1.22
Total costs (€)	**€8,368.51**	**€7,134.71**
Efficacy		
Survival (life years, LYs)	14.575	14.575
Quality of life adjusted survival (QALY)	11.114	11.019
Incremental outcomes (iStent *inject*® + cataract surgery vs. cataract surgery alone)		
Incremental costs (€)	€1,233.80	
Incremental LYs	-	
Incremental QALYs	0.095	
ICER (€/QALY)	€13,037/QALY	

LYs=life years; QALYs=quality-adjusted life years.

Sensitivity analysis

Both one-way deterministic and probabilistic sensitivity analyses confirmed the robustness and reliability of base-case results. The results of one-way deterministic analysis are summarized in Figure 2, that illustrates the 10 parameters / scenarios with the greatest effect on the ICER (base-case ICER: €13,037 / QALY). The ICER variability was modest (minimum ICER: €8,911/ QALY earned; maximum ICER: €24,764/ QALY gained).

The results of the probabilistic sensitivity analysis are reported in Figure 3 (acceptability curve of cost-effectiveness −CEAC-). The acceptability curve of cost-effectiveness (CEAC) analysis (Figure 3) showed that when the willingness to pay (WTP) is

equal to €50,000 per QALY gained, iStent *inject*® + cataract surgery would have a 98% probability of being cost-effective, compared to cataract surgery alone.

Discussion

Glaucoma is not only a major health problem, with a significant impact on patients' quality of life and social functioning, but also a relevant economic issue for healthcare systems [43]. Every year, glaucoma generates an expenditure of $2.5 billion of the US health care budget, of which $1.9 billion are direct medical costs [44]. Importantly, both the clinical and economic burden of the disease increase as glaucomatous damage and vision loss progress [43]. Therefore, any inefficiency in disease diagnosis, delayed treatment initiation, prolonged management with ineffective treatments, would translate into poor patient prognosis and increased costs for healthcare systems and society.

The recent technological advances in glaucoma management, specifically laser trabeculoplasty and micro-invasive glaucoma surgery (MIGS), offer ophthalmologists new options to manage POAG patients more effectively. Medical therapy has been the mainstay of glaucoma treatment for decades. However, medical treatment can be associated with adverse events, and some patients may be unable to comply adequately with complex dosing regimens [45].

iStent *inject*® seems one of the most exciting options among new treatments that could either replace or be used with medical therapy to optimize the management of mild-to-moderate glaucoma cases. The present cost-effectiveness analysis, conducted adopting the Italian National Health Service (NHS) perspective, shows that iStent *inject*® is a cost-effective option in patients with POAG, in need of simultaneous cataract intervention.

The cost-effectiveness analysis shows that a valuable QALY gain can be obtained with iStent *inject*® + cataract, with a modest economic investment. Although the use of iStent *inject*® does not seem to produce significant cost-offset (only a slight reduction of progression-related costs has been observed), the total incremental investments are quite low (+€1,234) and the overall lifetime costs are quite low as well (€8,369 per patient). These costs are much smaller if compared with those of other pathologies, where costs of ~€10K are sustained on an annual basis, rather than on a lifetime basis.

Moreover, the incremental cost-effectiveness ratio of €13,037 per QALY gained is significantly below the Italian informal acceptability threshold, amounting to €25-40 thousands per QALY gain [46].

Along with these economic considerations, there is a clear clinical rationale justifying the place in therapy of iStent *inject*® in glaucoma + cataract [5,14–17]. First, most of the evidence of iStent *inject*® regards POAG patients in need of cataract surgery. In this setting, it was showed that: i) device implantation is safe (i.e., negligible increase of adverse events, compared to cataract alone); ii) treatment in conjunction with cataract is more effective than cataract alone; iii) treatment effect is durable, thus postponing the need of more invasive glaucoma treatments, such as trabeculectomy.

The fact that iStent *inject*® can be performed during the cataract extraction, prolonging the primary intervention of a few minutes only, poses interesting economic considerations, since the procedural incremental costs associated with MIGS would be minimal in the hospital perspective.

Finally, iStent *inject*® implantation is a valid option to reduce the use of medical therapy. As explained earlier in the discussion, there is a critical, still unmet need of reducing the use of multiple, high-dosage medical treatment. In this context, clinical studies have demonstrated that IOP control can be achieved with iStent *inject*®, either without therapies or with a reduced number of therapies.

Overall, a thorough assessment of the methodological approach used to conduct this analysis is important to check validity of findings. In our view, adoption of conservative assumptions and generalizability of findings are two positive factors supporting the validity of the analysis. Whereas applicable, we opted for conservative assumptions, potentially underestimating cost-effectiveness of iStent *inject*® + cataract surgery. Likely, the most conservative assumption regarded the progressive reduction of IOP control over time (waning effect) for the two study treatments. In the model, a similar waning effect was assumed for

iStent *inject*® + cataract surgery and cataract surgery alone. While the progressive loss of therapeutic effect is clearly documented in literature for patients receiving cataract surgery [12], this might be delayed with iStent *inject*® + cataract surgery; however, no difference was modelled, given the uncertainty on this potential benefit. As regards generalizability of findings, instead, it should be remarked that the analysis is based on the randomized clinical trial (RCT) conducted by Samuelson et al 2019 [14], enrolling patients with 24.8 mmHg ± 3.3. This proves that iStent *inject*® + cataract was more effective than cataract alone in a large variety of patients, even in those with quite high IOP at baseline. Together with the above-mentioned analysis strength, a few limitations exist in this analysis, which must be analyzed and leave room for future improvement. First, someone could argue that a comparison between iStent *inject*® + cataract, vs. cataract followed by laser trabeculoplasty, would be more appropriate for decision-making processes. However, the lack of direct evidence comparing TBS vs. trabeculoplasty would make this comparison hard to conduct, to date. We expect this comparison would be critical for decision making in the future when appropriate evidence will be collected. Today, with the currently available information, we can only suppose that TBS might be either dominant or cost-effective than laser trabeculoplasty, because of the more robust long-term evidence, which is the main weakness of the latter [47].

Second, it would be interesting to conduct a cost-utility analysis of iStent *inject*®, looking at the social costs, rather than third-payer expenses only. Although results cannot be foreseen with certainty, we would expect that a social perspective analysis would be even more favourable to iStent *inject*®, than the current base-case analysis, because the difference in disease-related costs among the two groups would be more substantial. More cost-offset in the iStent *inject*® group would be generated.

The third, and probably most important point to assess would regard the economic sustainability of iStent *inject*® for hospitals. In our base-case analysis, the cost of the iStent inject® implantation was used in conjunction with cataract surgery: €2,294, (i.e. average of the tariffs of the procedure "Other interventions for glaucoma" [29 – 31] + iStent *inject*® acquisition costs). With these cost assumptions, iStent *inject*® + cataract was cost-effective vs. cataract alone. However, Italian hospitals are not receiving this remuneration for this combined intervention to date. Hospitals could obtain a remuneration of up to €1,522, which is the day-hospital intervention for glaucoma (DH 42 "Interventions on intraocular structures except retina, iris, and crystalline") [28]. In other words, with the current remuneration levels, hospitals would not be able to afford overall costs (iStent Inject®, cataract intraocular lenses, additional procedural charges -room, staffing, other equipment-, etc.). However, this intervention would be cost-effective for the Italian NHS. Our aim, with this paper, is then to make aware budget holders about this economic "paradox" and to evaluate solutions aimed at solving this issue. The future analyses on iStent Inject® should then assess both the NHS and hospital perspectives and verify whether results would be advantageous for both parties.

Finally, the glaucoma patient's population is extremely heterogeneous. We are aware that we have simplified conduct the analyses reported in this work. However, we can consider the results valid due to the robustness of the primary source and the conservativeness of the hypotheses made.

Conclusions

The results of the cost-utility analysis confirm that iStent *inject*® + cataract surgery is a cost-effective option for the treatment of patients affected by mild-to-moderate POAG, compared with cataract surgery alone, when evaluated from the Italian NHS perspective. Despite we are aware that modelling clinical outcomes and economic implications of treating the highly heterogeneous glaucoma patient population is a "simplification of reality" (all patients different to each other), the robustness of primary source and the conservativeness of the assumptions substantiate the validity of our findings.

Abbreviations

AEs: adverse events; **ALT/SLT**: laser trabeculoplasty; **CEAC**: acceptability curve of cost-effectiveness; **CI**: confidence interval; **dB**: decibel; **DH**: day hospital; **EMGT**: Early Manifest Glaucoma Trial; **HRQOL**: health-related quality of life; **IOP**: intraocular pressure; **ICER**: incremental cost-effectiveness ratio; **ISTAT**: Italian Institute of Statistics; **MD**: mean deviation; **MIGS**: micro-invasive glaucoma surgery; **MS**: market share; **NHS**: National Health Service; **NICE**: National Institute of Health Care and

Excellence; **OAG**: open-angle glaucoma; **POAG**: primary open-angle glaucoma; **QALY**: quality-adjusted life years; **RCT**: randomized clinical trial; **TBS**: trabecular bypass stent; **US**: United States; **VF**: visual field; **WTP**: willingness to pay.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

Furneri G.: consulting fees from Glaukos for analysis conduction.

Fea A.M.: consulting fees from Glaukos, Ivantis, ELTSight, iSTAR, and EyeD; travel fees from Johnson and Johnson, Allergan, and Sooft, outside the submitted work.

Authors' contributions

AMF and GF conceptualized the study. AMF and GF analysed data and developed the economic model.

GB reviewed the content of the economic analysis and approved it. AMF and GF drafted the first version of the manuscript. AMF, FC, SG, GB, GF, CC all contributed to the conception and refinement of the manuscript. GB reviewed the final content of the manuscript. All authors read and approved the final manuscript.

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