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Transparency section

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Declaration of financial/other relationship

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Author contributions

JEO was involved in formulation of the research question; protocol preparation; search, selection and evaluation of studies quality; quality control in data extraction; synthesis of the evidence; and manuscript writing.

AO was involved in model design; software programming; and manuscript writing.

UMO was involved in quality control in data extraction; synthesis of clinical evidence and costs; and manuscript writing.

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Abstract

Objective: To estimate cost-effectiveness of trabecular micro bypass stent versus laser trabeculoplasty or medications only, for patients with open-angle glaucoma in setting of Colombian System Health.

Methods: This is a cost-effectiveness analysis that based its assumptions in external data sources, used to extrapolate the quality of life related to health, survival and costs. A Markov model, with stages from 0 (ocular hypertension without glaucoma) to 5 and bilateral blindness, was developed inclusive of Colombian older than 40 years in 2018, from a societal perspective, comparing trabecular micro-bypass stents versus, laser trabeculoplasty, timolol+dorzolamide+brimonidine, timolol+dorzolamide+latanoprost, or timolol+dorzolamide+brimatoprost, in terms of clinical and economic outcomes over a lifetime horizon. Both costs and health outcomes had an annual rate discount of 5%. Health outcomes were evaluated in terms of QALYs related with loss of visual acuity. Trabecular micro-bypass costs include the joint use of timolol, the costs of laser trabeculoplasty include the combined use of timolol+dorzolamide.

Results: Trabecular micro-bypass stents were estimated to have 127,971 more discounted QALYs, versus laser trabeculoplasty; 405,982, versus timolol+dorzolamide+brimonidine; and 378,287, versus timolol+dorzolamide+latanoprost or timolol+dorzolamide+brimatoprost. Cumulative costs with trabecular micro-bypass stents at 40 years was $13,252,318 lower than laser trabeculoplasty; $6,403,534, lower than timolol+dorzolamide+brimonidine; $22,311,064, lower than timolol+dorzolamide+latanoprost; and $29,156,113 lower than timolol+dorzolamide+brimatoprost.

Conclusions: Trabecular micro-bypass stent is a highly cost-saving strategy due to more QALYs related to a lower rate of the population with loss of visual acuity in the long term, and because the costs associated with additional medications and complications are lower with trabecular micro-bypass stents.

Keywords: cost-benefit analysis; open-angle glaucoma; ocular hypertension; stents; minimally invasive surgical procedures; medication adherence

Short title: Cost-effectiveness of trabecular micro-bypass stent in Colombia

Introduction

Open-angle glaucoma (OAG) represents approximately 70 % of glaucoma cases in the world. Its prevalence has been increasing, probably due to the increase and improvement of diagnostic technology methods [1]. World prevalence of glaucoma in people between 40 and 80 years was estimated at 64,3 million in 2013, and it is projected that by 2020 it will increase to 76 million people [2]. There are many estimates of glaucoma prevalence that differ among them, mainly because of the differences in age and racial structures of the populations. The prevalence adjusted for age shows that, in African-American people, this is four to five times higher than in non-Hispanic whites. A population-based study showed that the annual incidence of OAG in a population of white majority in the USA, is 14.5 per 100,000 people, which increases with age, going from 1.6 per 100,000 in fourth decade of life to 94.3 per 100,000 people in life eighth decade [3].

In Latin America there are not many epidemiological studies that quantify prevalence of glaucoma, however, there are data from different studies in some countries of the region, either

hospital-based or derived from screening studies. In Peru, a glaucoma prevalence of 1.9 % was estimated in patients older than 30 years, diagnosed by indentation tonometry and direct funduscopy [4]. In the RACSS study in Brazil, it was found that 11.4 % of blindness is attributed to glaucoma [5]. However, this prevalence was higher in patients older than 50 years, in which 20 % of cases of blindness were attributed to glaucoma [6]. In an ophthalmologic hospital in Ecuador, was observed a blindness prevalence of 17 % related to glaucoma, but this could be due to the way of selecting the sample, because that study is not based in general population [7]. Visual health situation in Colombia found out 238,846 people with glaucoma generate 450,084 health care activities, representing 0.08 % of total health care in the country (8).

Proven treatment to reduce glaucoma risk progression is to decrease intraocular pressure (IOP) through topical medications. Among most commonly used are prostaglandin analogs, β-adrenergic agonists, carbonic anhydrase inhibitors, α-adrenergic agonists, and miotic agonists, such as pilocarpine [9]. Although monotherapy is most usual strategy at disease beginning, as the severity of glaucoma increases, different combinations of these medications are used. Main problem faced by patients, besides to polypharmacy secondary effects, is noncompliance medication and their insufficient ability to apply them, which affects clinical effectiveness. Surgical procedures such as selective laser trabeculoplasty have shown good clinical outcomes. Recent use of trabecular micro-bypass stent by means of minimally invasive glaucoma surgery (MIGS) has shown great outcomes.

As glaucoma is a chronic disease whose damage to optic disc is not reversible, it is necessary to consider different treatment strategies in a scenario that evaluates both costs and clinical outcomes during patients lifetime horizon, with the purpose of generating information that allow to decision makers to identify treatment strategy that offers best clinical outcomes, adjusted to economic reality of Colombian health system.

Methods

Target population

Patients with mild to moderate glaucoma, includes visual field defects or characteristic optic nerve abnormalities consistent with mild to moderate glaucoma and cup-disk ratio no worse than 0.8, and with a medicated IOP of 24 mmHg of less, receiving from one to three medications. Patients with angle-closure glaucoma, secondary glaucoma (except pseudoexfoliative and pigmentary), severely uncontrolled IOP, severe glaucomatous field defects, previous glaucoma surgery (except iridectomy), with previous refractive procedures, and monocular patients or patients with visual acuity (VA) corrected lesser than 20/200 in the other eye, were excluded.

Study perspective

The perspective of the analysis is from the General System of Social Security in Health of Colombia, this implies identifying the direct costs of the resources associated with the use of these technologies, included or not in the Plan of Benefits of Health of Colombia [10], and the health outcomes perceived by patients.

Comparators

Trabecular micro-bypass stent through the MIGS targets three main flow channels: the suprachoroidal space through uveoscleral pathway, Schlemm channel through trabecular flow, and subconjuntival space, thus creating an alternative flow path for aqueous humor, with an approach internal and minimal trauma, being a very safe procedure with a patient quick recovery. Goal of this surgery is to fill gap between medical treatment and more invasive surgeries such as trabeculectomy [11]. Many micro-invasive surgeries are performed simultaneously with cataract surgery. iStent®, an intraocular stent manufactured in titanium and covered with heparin in an L-shaped structure, is one of most widely used and studied micro-invasive surgery devices.

Prostaglandin analogs are commonly used as first line treatment due mainly to lack of systemic side effects and convenience of daily dose, except for unoprostone, which usually promotes adherence. They are contraindicated in patients with reactive airway or with renal failure. Adverse effects of this group of medications include ocular hyperpigmentation, conjunctival injection, allergic conjunctivitis, contact dermatitis, keratitis, possible reactivation of the herpes virus, uveitis, increased pigmentation of the iris, cystoid macular edema and periorbitopathy [12].

β-adrenergic agonists are currently most used group of topical medications. There are two classes of β-blockers, nonselective ones that bind to β1 and β2 receptors and include timolol maleate, hemihydrate, levobunol, carteolol and metipranolol. Mechanism by which blockade of β-

receptors leads to a decrease in production of aqueous humor and consequently to a reduction in IOP, is not known. Apparently, aqueous humor production is activated by a cyclic AMP-PKA pathway mediated by β receptors [13]. Possible side effects include keratitis, allergic conjunctivitis, bronchospasm, depression hypotension, bradycardia, etc. [12].

α-adrenergic agonists activate α1 receptors that simulate contraction of iris dilator muscle Müller muscles, leading go mydriasis and retraction of eyelid. Also, α1 stimulation leads to vasoconstriction, which results in restricted blood flow to ciliary muscle and a reduction in aqueous humor production [14]. Among its possible adverse effects are allergic and follicular conjunctivitis, hypotension, fatigue, headache and somnolence [12].

Carbonic anhydrase inhibitors were initially introduced as effective oral diuretic agents, subsequently used for glaucoma treatment, and have been found to lower IPO by reducing aqueous humor production in ciliary body [15]. For a long time, systemic treatment with carbonic anhydrase inhibitors was one of most important components for glaucoma treatment, however, it lost importance with introduction of the topical form in 1995. Systemic drug is currently reserved for short term treatments in patients with maximum doses of medical therapy, or when other treatments have not achieved the patient' goal to decrease IOP. Potential adverse effects of this therapy include corneal edema and keratitis [16].

Pilocarpine ophthalmic is a natural alkaloid obtained from *Pilocarpus Jaborandi* leaves, and its effect on dynamics of aqueous humor is complicated and not completely understood. It is

believed that main mechanism to reduce IOP is flow increase, in the same way, parasympathetic-mimetic stimulation contracts ciliary muscle and produces an internal movement of scleral spur to which it is attached. This produces a structural change in trabeculum, allowing an increase in aqueous flow. IOP reduction begins 60 minutes after its application and peaks at 75 minutes, lasting four to eight hours, depending on dose [17]. However, these parasympathetic-mimetic agents could produce adverse effects such as increased myopia, cataracts, periocular dermatitis, allergic conjunctivitis, decreased VA, conjunctival contraction, conjunctival scars, keratitis, among others [12].

Selective laser trabeculoplasty works in the same way as argon laser trabeculoplasty, flanking the trabecular meshwork by means of an Nd YAG laser applying shocks of shorter energies, causing less damage. This surgery is a good option for elderly patients with little adherence or low tolerance to topical medication, and who are not candidates for trabeculectomy. It is a relatively non-invasive procedure that takes approximately 10 to 20 minutes. A systematic review of 19 studies showed that there is no significant difference between laser-selective trabeculoplasty and argon laser trabeculoplasty when comparing decrease in IOP [18].

Time horizon

Although there are trials with trabecular micro-bypass stent with up to four years of follow-up [19], most of clinical trials about drugs for ocular hypertension treatment are followed for three months and some for up to one year. Although the natural history of glaucoma exceeds this time, it was not possible to obtain randomized controlled trials (RCTs) that considered a longer time

horizon that would have impact on clinical outcomes. We consulted with clinical experts about time horizon that could reflect in a better way of treatment strategies effectiveness evaluated in the model, who agreed to structure it with population lifetime horizon, with decision points every year, to evaluate mortality rate. This time horizon is necessary because this is a chronic disease that can start when patients are still young adults and they are going to suffer it throughout all their lives.

Discount rate

A discount rate of 5 % was used for both costs and benefits. This is considered the discount rate that best fits Colombian context and is also discount rate recommended by Institute of Technological Evaluation in Health in Colombia [20].

Choice of health outcomes

Three outcomes were chosen; first, hip fractures avoided due to VA loss; second, Life-Years Gained (LYGs) for premature deaths avoided due to hip fractures; third, lost Quality Adjusted Life-Years (QALYs) by VA decrease and loss. QALYs allow to capture both Quality of Life (QoL) related with health and time, that is, a qualitative variable and a quantitative variable simultaneously, this is so important because glaucoma is a chronic disease and its treatment' goal is to decrease losing vision risk during patient's life. About clinical outcomes, an adjustment by loss of QALYs due to chronic noncommunicable diseases was made, based on a study that found out QALYs loss in patients between 20 and 80 years of age with cataracts [21].

Measurement of effectiveness

Several systematic reviews were carried out to identify clinical efficacy, using same search strategy for each comparator, which included the MeSH term for each drug or laser selective trabeculoplasty, and term primary OAG (POAG). We searched for metanalysis of RCTs; in case they were not obtained, we searched for RCTs that met GRADE bias control criteria [22].

Estimating resources and costs

A search was made of individual costs of all interventions, procedures and medicines required from database of a Health Maintenance Organization (HMO) of Colombia, with a national presence and with data for year 2017. Drug Price Information System of Colombia (SISMED, Spanish acronym) was used to take drug costs for ocular hypertension treatment, and weighted mean was calculated for every strategy evaluated. Then, costs were estimated for each one drug strategy for ocular hypertension treatment, as well as costs of ophthalmological surgeries and hip arthroplasty in individual with hip fracture due to VA loss (Table 1). For costs calculation in patients undergoing ophthalmic or orthopedic surgery, a top-down methodology was used, based on hospital invoices of HMO.

Currency, price data, and conversion

Costs are originally calculated in Colombian pesos (COP) and later were converted into American dollars (USD), based on a mean exchange rate of COP 3,000 for USD 1.

Choice of model

This is a cost-effectiveness decision model with a Markov structure to estimate costs and long-term health outcomes (Figure 1). Model structure is based on natural history of ocular hypertension and its relationship with POAG. Model stages of are based on paper of Mills et al about glaucoma categorization from disease pre-diagnosis to its final state [23], which is currently most used to describe glaucoma natural history. Model includes entire population over 40 years old with ocular hypertension, with or without treatment. Annual Markov cycles are applied in a patient cohort progressing through Markov model, according to estimated transition probabilities.

Given that duration of most RCTs evaluating drug's efficacy for ocular hypertension treatment are three months and that model' cycles last one year, it is assumed that patients will be evaluated four times by ophthalmologist during each cycle, at which time, probability of continuing in same stage, changing status or dying, will apply. Model does not assume glaucoma deaths, so death probability of model is mortality rate of general population. Model has 40 cycles from when individuals enter until they die with a lifetime horizon of 80 years. Cohort of model is dynamic during the 40 cycles, this means that individuals who are under 40 years old at time of model initiating, will enter when they are 40 years old.

Assumptions.

This decision model considers following assumptions with respect to comparators:

- In all patients with MIGS for implantation of a trabecular micro-bypass stent, it is assumed that they continue to receive timolol during their lifetime horizon.
- In all patients with laser trabeculoplasty surgery, it is assumed that they continue to receive timolol + dorzolamide during lifetime horizon.
- All patients with medicines only, receive two or three drugs simultaneously; it is assumed that no one receive monotherapy because of its high failure treatment rate.
- Combinations of two or three drugs estimated in this decision model, which are assumed to be most used by ophthalmologists, are:
    - Latanoprost + Timolol + Dorzolamide
    - Bimatroprost + Timolol + dorzolamide
    - Travoprost + Timolol + Dorzolamide
    - Brimonidine + Timolol + Dorzolamide
    - Timolol + Travaprost
    - Timolol + Travaprost (Bak Free)
    - Timolol + Brinzolamide
    - Timolol + Brimonidine
    - Brimonidine + Brinzolamide

Analytic methods.

Survival analysis was used to determine risk of every clinical pathway and to derive Markov cycles probabilities. Drug adverse events ocular hypertension treatment are not modeled because most of it disappear quickly when medication is interrupted, so cost structure is not affected.

Model has two main features: the QALYs adjustment over time, and hip fracture as a complication related to VA reduction. QALY adjustment over time is justified by impact of chronic noncommunicable diseases (NCDs) over burden of disease in world. For this purpose, a study that estimated QALYs loss in adults from South Korea according to 13 NCDs in 2010, including cataracts, was used. This study found out that when weighting utility for some NCDs according to sex and age, in some cases utility did not decrease as the age increased, for example, myocardial infarction in women between 20 and 29 years old. On the other hand, NCDs most affect QALYs loss due to morbidity are cataracts, hyperlipidemia and depression [21]. Importance of this concept is that, most times, lost QALYs increase as the population ages, therefore QALYs change over time.

Regarding hip fracture as an outcome of this model, it is justified because falls, particularly associated with injuries, are a problem of public health for elderly in the world. About 30 % of people over 65 have a fall at least once a year, 10 % - 20 % of these falls cause injuries and 5 % - 6 % result in fractures [24]. In 2010, there were 21,649 deaths due to falls among people > 65 years in US [25]. Falls are not only associated with physical consequences, they are also associated with a decrease in quality of life and other events, such as depression, fear of another fall, restricted activity, hospitalization and subsequent admission to a nursing home. Greater risk

of falls in elderly is aggravated by visual impairment, and this has been a consistent finding in several studies [26-28].

In fact, a metanalysis found that relative risk of a fall in people whose visual impairment was caused by visual field loss or glaucoma, was greater compared to population with general disability [29]. A recent study showed that best corrected VA in the eye and in worst eye of patients with POAG was significantly associated with falls [26]. Some studies have reported that VA in worst eye is a risk factor for falls in elderly [30,31].

Finally, considering that glaucoma is a NCD that still has no cure, whose treatment is aimed at reducing disease worsening rate and that involves daily application of several medicines, has a problem of nonadherence to treatment, which affects its clinical effectiveness and model outcomes. Adherence or compliance to a medication regimen is generally defined as extent to which patients take medications as prescribed by their health care providers [32]. Noncompliance can be due to failures in form of taking a medication, doing it at wrong time, taking an incorrect medication or, rarely, taking them excessively. However, in ocular diseases, noncompliance could even result from an inadequate technique of medication administration.

Results

Study parameters.

Model allows to adjust frequency distribution of glaucoma according to disease severity level and patients age group. In this cost-effectiveness analysis, it was decided to start with 100 % of population in stage 0 (zero), that is, with ocular hypertension, with minimal or no defect, and that they do not meet criteria required for disease stage 1 according to Mills et al [23]. Disease prevalence assumes distribution indicated in Visual Health Situation Analysis of Colombia in 2016 (Table 2) [8]. Clinical outcome of model was patients rate who had a decrease > 20 % in baseline IOP, measure reported by most RCTs. Table 3 shows mean, minimum and maximum values of clinical efficacy of each one strategy.

Drugs adherence for ocular hypertension treatment in this model was determined in 50 %, which was established based on four clinical studies that had different values: Okeke et al, 54 % [54]; Gupta et al, 10 % [55]; Campbell et al, 33.9 % (bimatoprost 0.03 %) to 48.8 % (bimatoprost 0.01 %) [56]; and Barnebey et al, 32 % [57]. Transition annual probabilities between the five stages of glaucoma were taken from a study about resources use according to disease severity level (Table 4) [58]. In the same way, risk of developing unilateral blindness without treatment is 40.5 %, and bilateral, 16.5 %, according to a mathematical model that estimates glaucoma progression [59]. QALYs were taken from a cross-sectional study done in US that calculated utilities for five ophthalmological diseases, according to disease severity level (Table 5) [60].

QALYs for VA loss caused by glaucoma were adjusted during patients' lifetime horizon, based on calculation made by Ock [21]. Hip fracture incidence in older adults, adjusted by age group, was taken from Dirani et al, as follows: 60 – 69 % years, 0.10 %; 70 – 79 years, 0.40 %; and >

80 years, 1.90 % [29]. From the same study, risk ratio (RR) of having a hip fracture according to glaucoma clinical stage in comparison with healthy people, was taken (Table 6), which was only applied to patients > 60 years of age, who have a higher risk of fall and fracture. Likewise, hip fracture lethality risk was taken from CHANCES project, that evaluated mortality excess from this cause in older adults in US and Europe [61], expressed as Hazard Ratio (HR) (Table 7), which was used for adjusting general mortality rate of Colombia, according to National Administrative Department of Statistics report (DANE, in Spanish) [62].

Finally, Gupta et al [55] found out that in patients with glaucoma who had more than six months of treatment, waste of ophthalmic drops due to failure by its application is 38 %. This value was applied to amount of medicines used by patients every year, thus adjusting healthcare costs for population with glaucoma.

Incremental costs and outcomes.

These are deterministic results of base case, comparing cost-effectiveness ratio of trabecular micro-bypass stent versus selective laser trabeculoplasty surgery and different medications combination for ocular hypertension treatment (Table 8). Trabecular micro-bypass stent is a dominant strategy versus all other treatment strategies of POAG. iSent® total costs discounted during population lifetime horizon are lower than those of other comparators. Likewise, discounted QALYs of trabecular micro-bypass stent in this population are greater than those of all other comparators, this means that versus laser selective trabeculoplasty and all medications

schemes for ocular hypertension treatment, total costs of iStent® are lower and its QALYs are higher.

Characterizing uncertainty.

It has been suggested a discount rate of 5 % in Colombia (which was applied in the results of table 8), but really there is no empirical argument to ensure what is ideal value to make this calculation. For this reason, results of this evaluation are presented with different discount rates: 3.5 % (Table 9) and 10 % (Table 10). In the same way, we have estimated ICER through a one-way analysis with the minimum and maximum effectiveness (Table 11) and costs (Table 12) of every strategy.

To evaluate model robustness, a probabilistic sensitivity analysis was performed through a Monte Carlo simulation with 5,000 iterations. These results are reported through bivariate analyzes between trabecular micro-bypass stent versus every comparator by means of tornado diagrams (Figures 2-11), as well as through multivariate analysis using cost-effectiveness plane (Figure 12) and willingness-to-pay curve (Figure 13).

Discussion

Trabecular micro-bypass stent (+ timolol) is a dominant strategy versus trabeculoplasty laser surgery (+ timolol + dorzolamide) and the different medicines schemes for POAG treatment in Colombia. Discounted total costs with trabecular micro-bypass stent strategy after follow-up

during population lifetime horizon were $ 22,018,077 and discounted total QALYs were 2,226,612. These costs were lower than those of all comparators and QALYs were higher than those obtained by any of other strategies. Strategy most bring closer to micro-bypass stent in terms of costs was brimonidine + timolol + dorzolamide, whose discounted total costs were $ 28,422,312; all other strategies had higher costs. Likewise, strategy that most approached to trabecular stent with respect to QALYs was laser surgery + timolol + dorzolamide, which obtained 2,098,641 QALYs.

This result remains constant in scenarios with different discount rates, both lower and higher than 5 %, which was the value used in base case scenario. With a discount rate of 0 %, total discounted costs of trabecular micro-bypass stent were $24,511,411 and its total discounted QALYs were 3,438,382, this trabecular stent being the strategy with the lowest costs and highest QALYs. With a discount rate of 3.5 %, total discounted costs of trabecular micro-bypass stent were $22,522,209 and its total discounted QALYs were 3,382,719. Again, trabecular micro-bypass stent was strategy with lowest cost and highest QALYs (Table 9). Based on above, it can be assumed that discount rate does not affect results of base case, that is, trabecular micro-bypass stent is a dominant strategy versus the other strategies, regardless of discount rate.

In one-way sensitive analysis (OWA), when assigning maximum effectiveness value to every comparator versus mean effectiveness of trabecular micro-bypass stent (69.1%), results obtained in base case do not change, trabecular micro-bypass stent continues being dominant versus all other comparators. Comparator with a higher effectiveness is selective trabeculoplasty laser +

timolol + dorzolamide, which has a maximum effectiveness of 29 %. Similarly, when assigning minimum value of effectiveness to trabecular micro-bypass stent (58.7 %) versus the mean effectiveness of all other strategies, there were no changes in results with respect to those observed in base case, in which trabecular micro-bypass stent is dominant versus all other comparators (Table 11).

Continuing with OWA, when assigning minimum cost to every comparator versus mean cost of trabecular micro-bypass stent ($ 1,417, the first year), this strategy is still dominant versus all comparators. The comparator with a lower cost than others, is the combination brimonidine + timolol + dorzolamide ($ 311). Similarly, when assigning maximum cost to trabecular micro-bypass stent versus mean cost of all other strategies evaluated, there were no changes in the results versus the base case, in which trabecular micro-bypass stent is dominant versus the other comparators (Table 12). In bivariate analysis, which compares each one result of trabecular micro-bypass stent versus every strategy, costs and effectiveness of each strategy had the greatest weight on cost-effectiveness.

About multivariate sensitivity analyzes, in cost-effectiveness plane, trabecular micro-bypass stent was in center of plane and all other strategies were in northwest quadrant, that is, all strategies were dominated by the trabecular micro-bypass stent, since their costs were higher and their QALYs lower versus trabecular micro-bypass stent (Figure 12). In willingness-to-pay curves, trabecular micro-bypass stent had a 100 % probability of being the chosen strategy, with any availability value to pay (Figure 13).

Results of sensitivity analysis shows robustness of results of base case, since in all scenarios dominance of trabecular micro-bypass stent (+ timolol) is maintained versus laser selective trabeculoplasty (+ timolol + dorzolamide) and all combinations of medicines for ocular hypertension treatment, included in this economic evaluation. That is, trabecular micro-bypass stent is a cost-saving strategy for treatment of patients with POAG in Colombia. Although its cost is higher in first year, total discounted costs are lower at end of follow-up, since this higher cost is due to device that is implanted only once versus other strategies that must use simultaneous combination of several medications throughout patient's lifetime horizon, which have less clinical efficacy and that generates more costs due to the complications related to VA loss, such as hip fracture.

Trabecular micro-bypass stent is a technology that has been evaluated for a decade, and although there is profuse literature about its safety and clinical efficacy, there are still few economic evaluations on it. Recently, Berdahl et al published a cost study in which they compared this trabecular micro-bypass stent with the selective laser trabeculoplasty or drug treatment, in which they found that, despite its higher costs in year zero, thereafter, they were lower yearly in patients with trabecular micro-bypass stent. For this reason, authors concluded that trabecular micro-bypass stent can reduce use of health resources in relation to POAG, which generates direct savings, especially regard to medications in time horizons of more than one year [63], results that are like those of this economic evaluation.

During question refinement, there were sociodemographic considerations related to complications about disease natural history. For this purpose, Dirani study [29] was considered about economic impact of glaucoma in Australia, in which authors considered risk of falling and hip fracture due to decreased VA. Although a variety of economic studies have been published about diagnostic and treatment strategies for POAG management (Berdahl et al [63], Pizzi et al [64], Javanbakht et al [65], Boodhna et al [66], Kaplan et al [67], Patel et al [68], among others), none has considered hip fracture outcome due to VA loss as an outcome directly related to POAG. This outcome was considered because population most affected by POAG are > 40 years, and population with highest risk of hip fracture are adults > 60 years.

Main limitation of this economic evaluation is follow-up of population during their lifetime horizon, which for this study is 80 years, that means that this follow-up lasted a maximum of 40 years. For such a long-time uncertainty is greater; because although it is unlikely that clinical efficacies of these technologies will change, the other variables can do it. During this period, prices of all strategies can decrease (it is foolhardy to establish magnitude of such decrease); lifetime horizon is likely to increase, which would increase risk of hip fracture; diagnosis and treatment of hip fracture could change in elderly; new technologies will generate previously unknown information. These uncertainties would affect all comparators equally, thus reducing risk of bias that they generate about results of this study.

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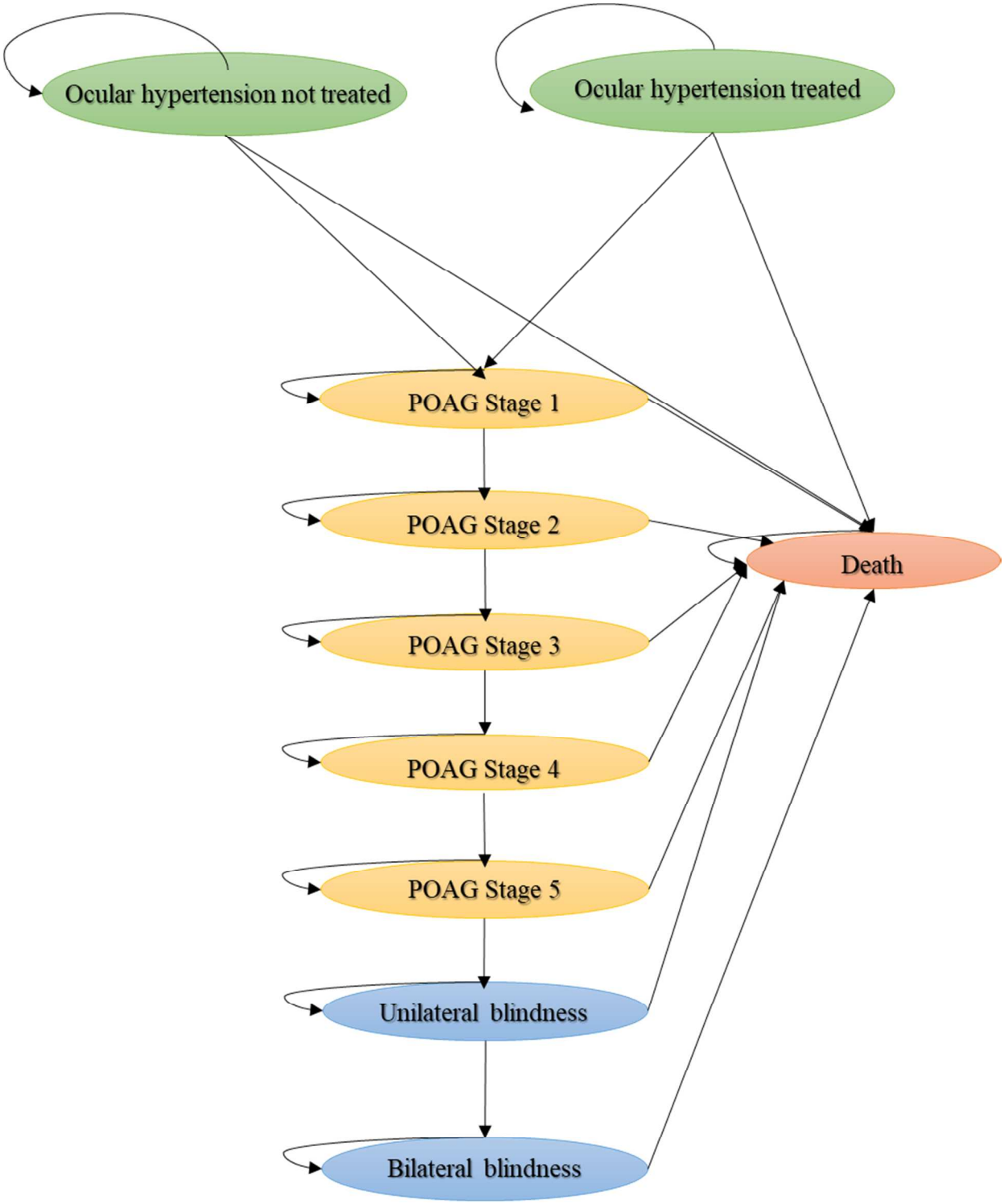


Figure 1. Structure of Markov decision model of patients with POAG during lifetime horizon, adapted from categorization of glaucoma natural history, by Mills et al (23).

Figure 2. Diagram of tornado of micro-bypass trabecular stent versus selective laser trabeculoplasty for treatment of POAG in Colombia, 2018

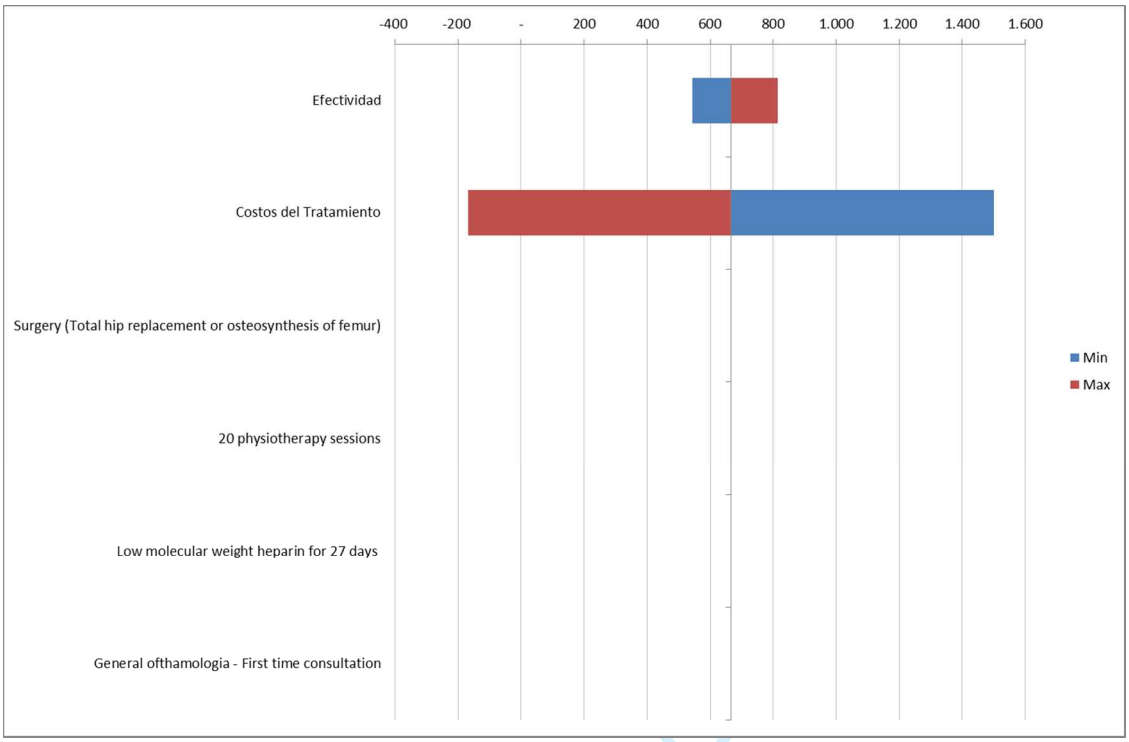


Figure 3. Diagram of tornado of micro-bypass trabecular stent versus medical treatment with latanoprost + timolol + dorzolamide for treatment of POAG in Colombia, 2018.

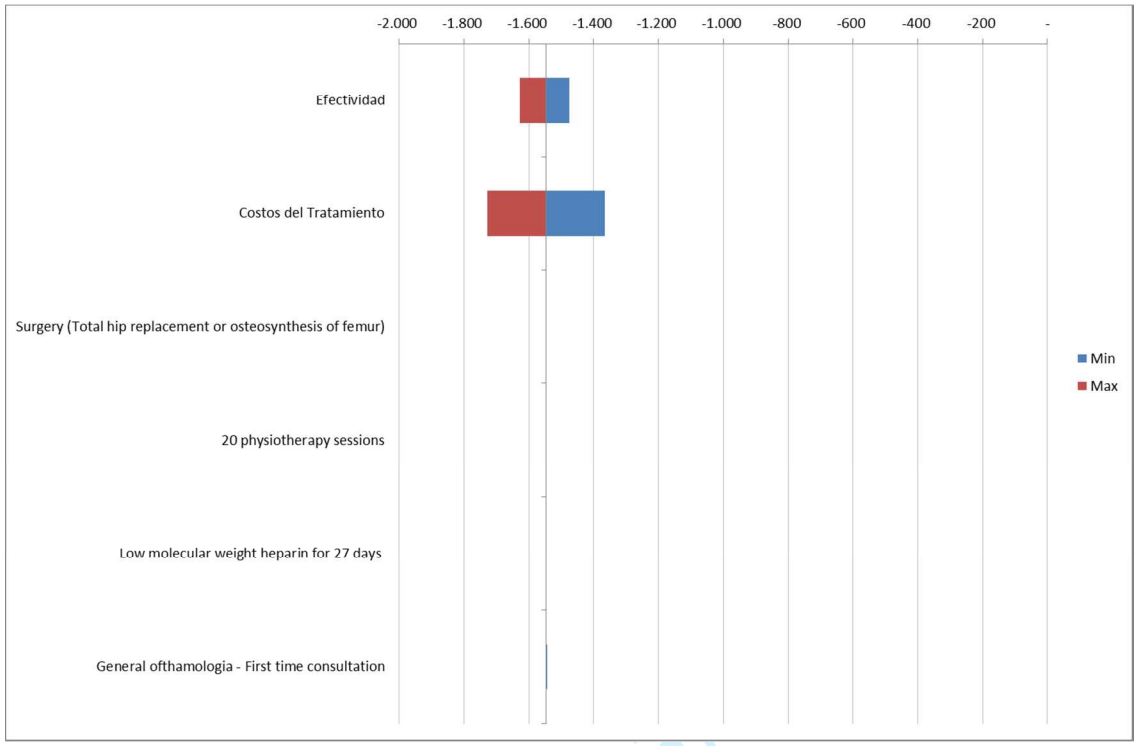


Figure 4. Diagram of tornado of micro-bypass trabecular stent versus medical treatment with bimatoprost + timolol + dorzolamide for treatment of POAG in Colombia, 2018.

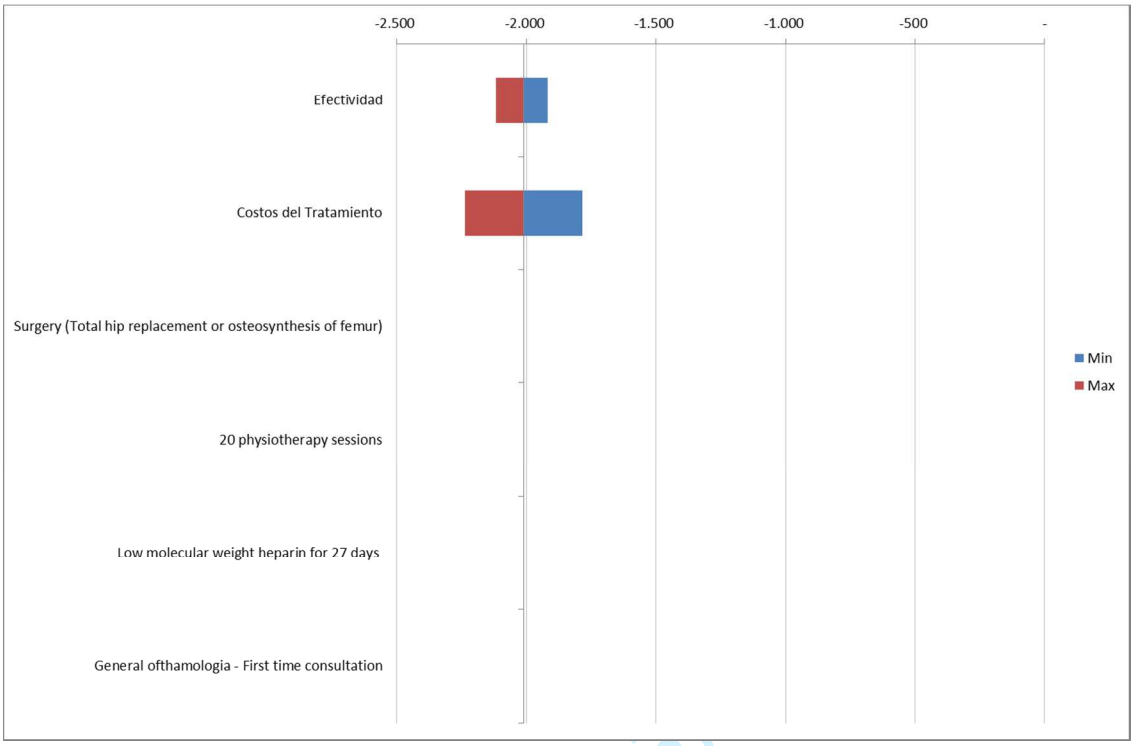


Figure 5. Diagram of tornado of micro-bypass trabecular stent versus medical treatment with travoprost + timolol + dorzolamide for treatment of POAG in Colombia, 2018.

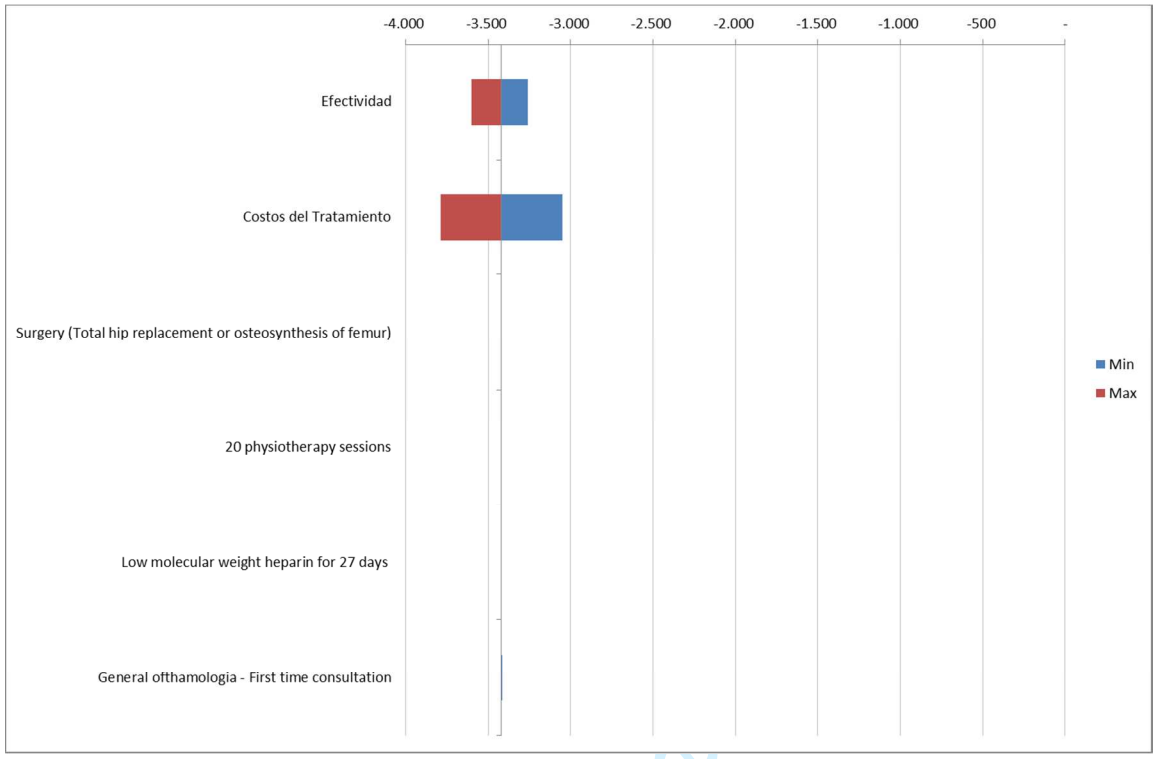


Figure 6. Diagram of tornado of micro-bypass trabecular stent versus medical treatment with brimonidine + timolol + dorzolamide for treatment of POAG in Colombia, 2018.

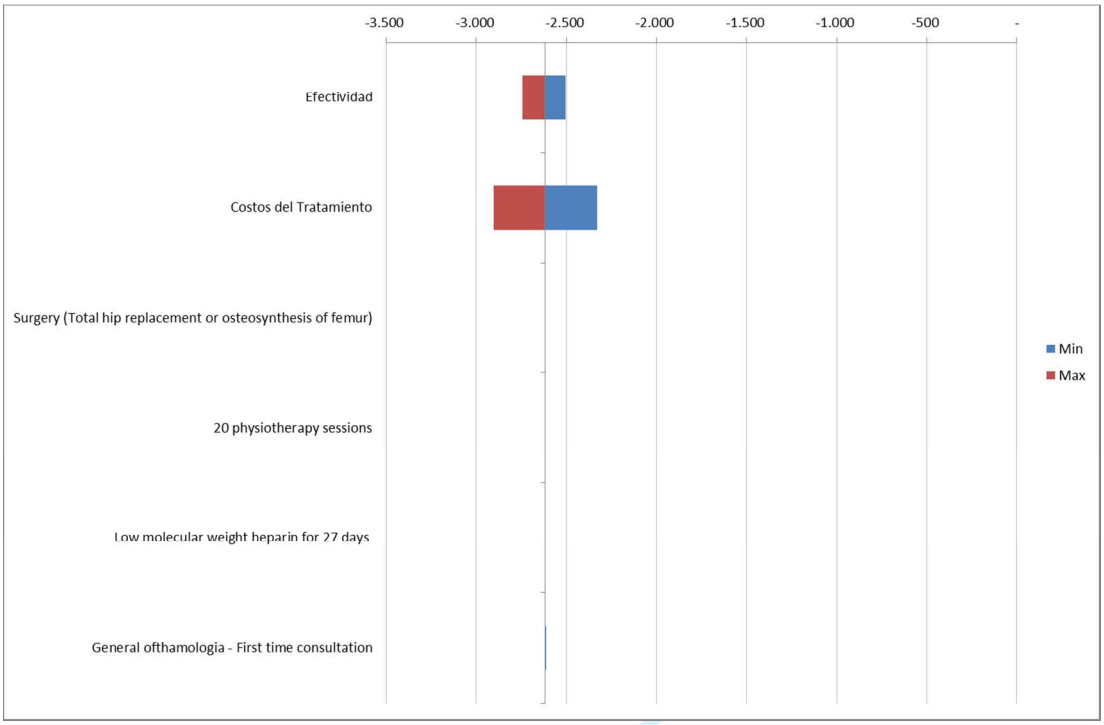


Figure 7. Diagram of tornado of micro-bypass trabecular stent versus medical treatment with timolol + travaprost for treatment of POAG in Colombia, 2018.

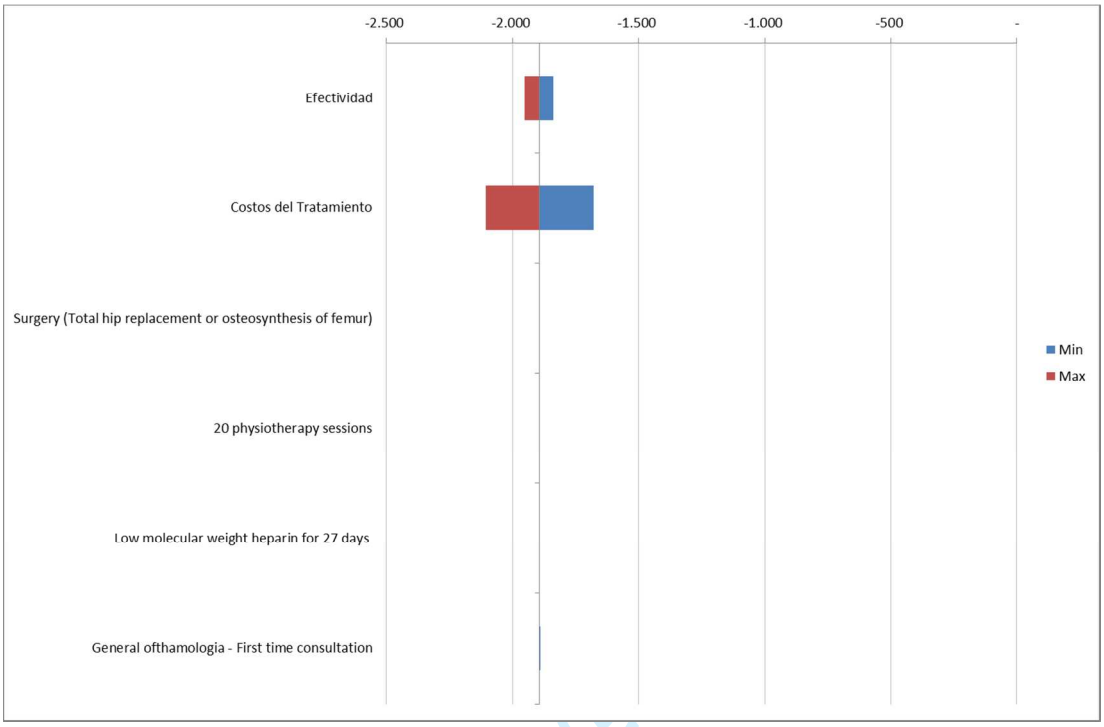


Figure 8. Diagram of tornado of micro-bypass trabecular stent versus medical treatment with timolol + travaprost (Bak Free) for treatment of POAG in Colombia, 2018.

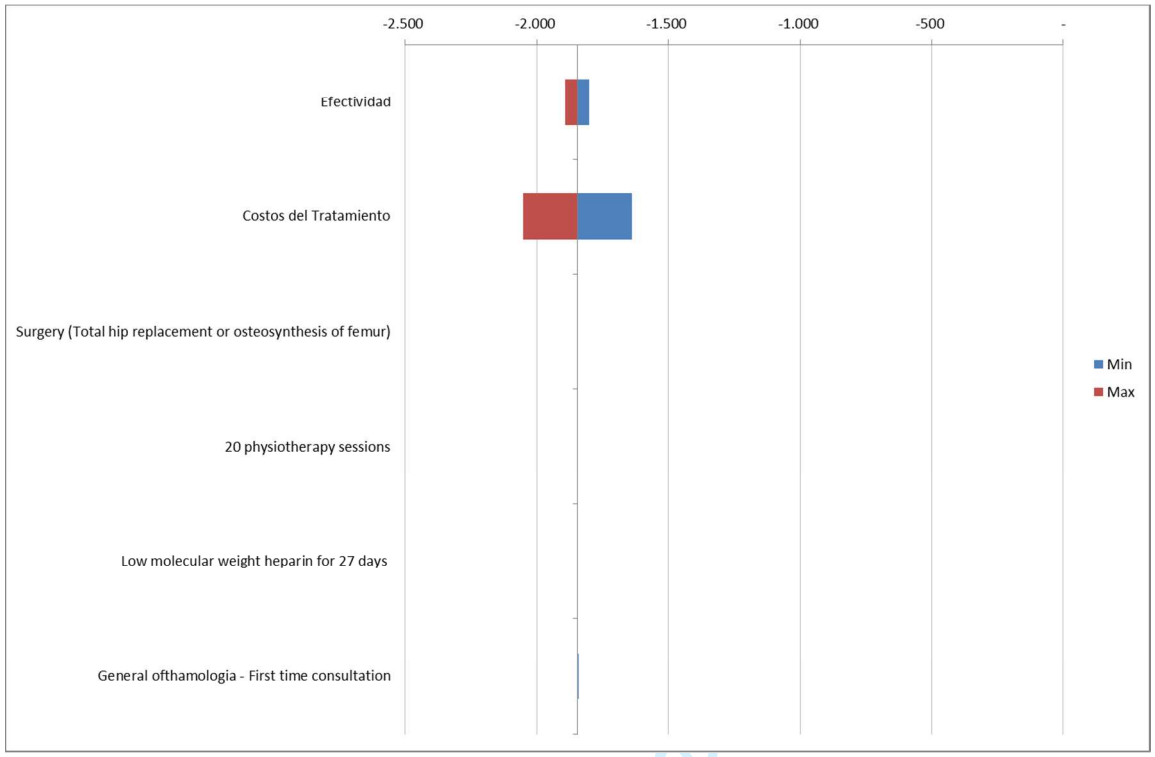


Figure 9. Diagram of tornado of micro-bypass trabecular stent versus medical treatment with timolol + brinzolamide for treatment of POAG in Colombia, 2018.

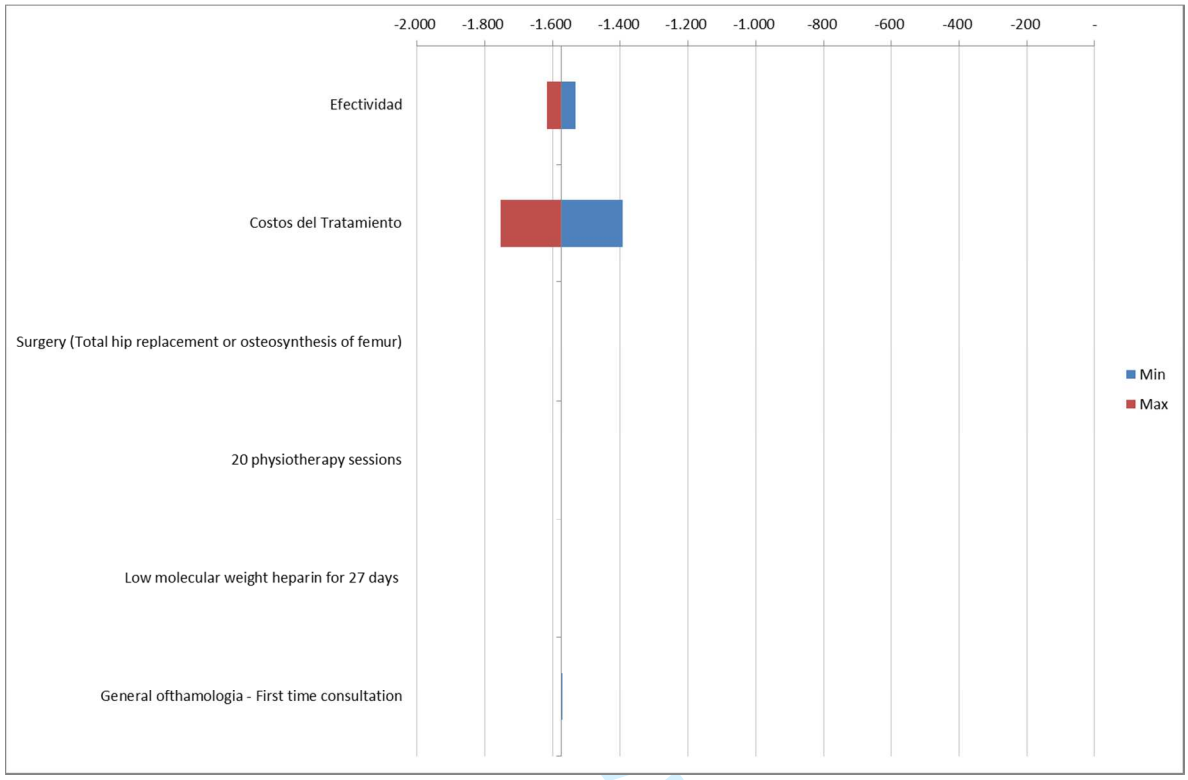


Figure 10. Diagram of tornado of micro-bypass trabecular stent versus medical treatment with timolol + brimonidine for treatment of POAG in Colombia, 2018.

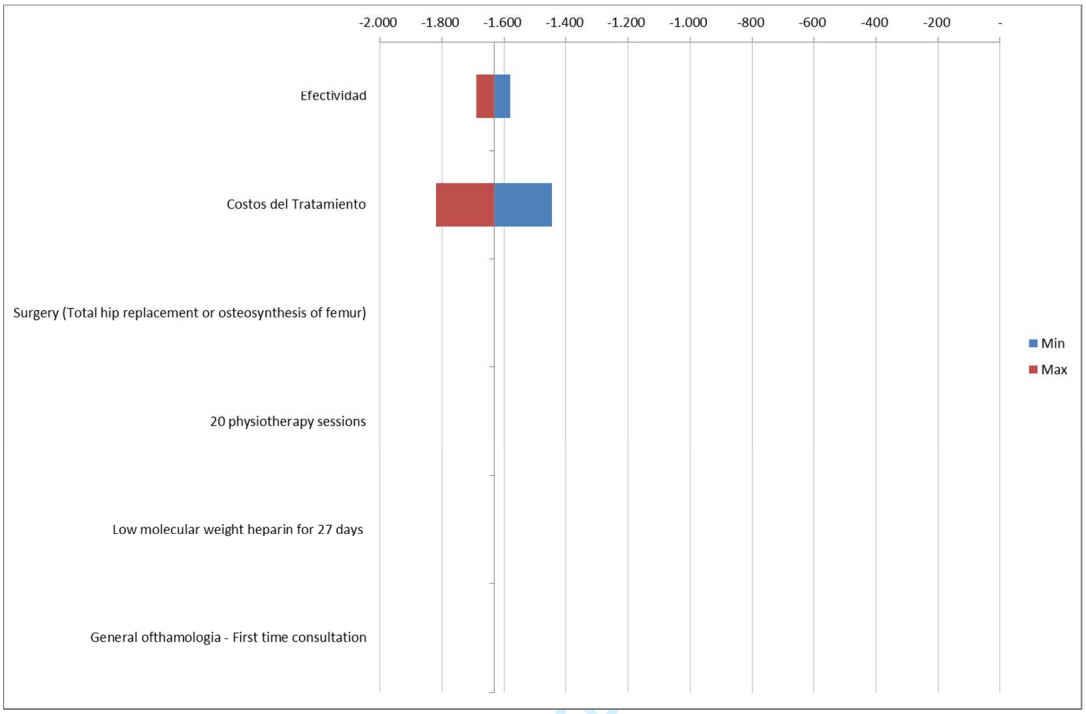


Figure 11. Diagram of tornado of micro-bypass trabecular stent versus medical treatment with brinzolamide + brimonidine for treatment of POAG in Colombia, 2018.

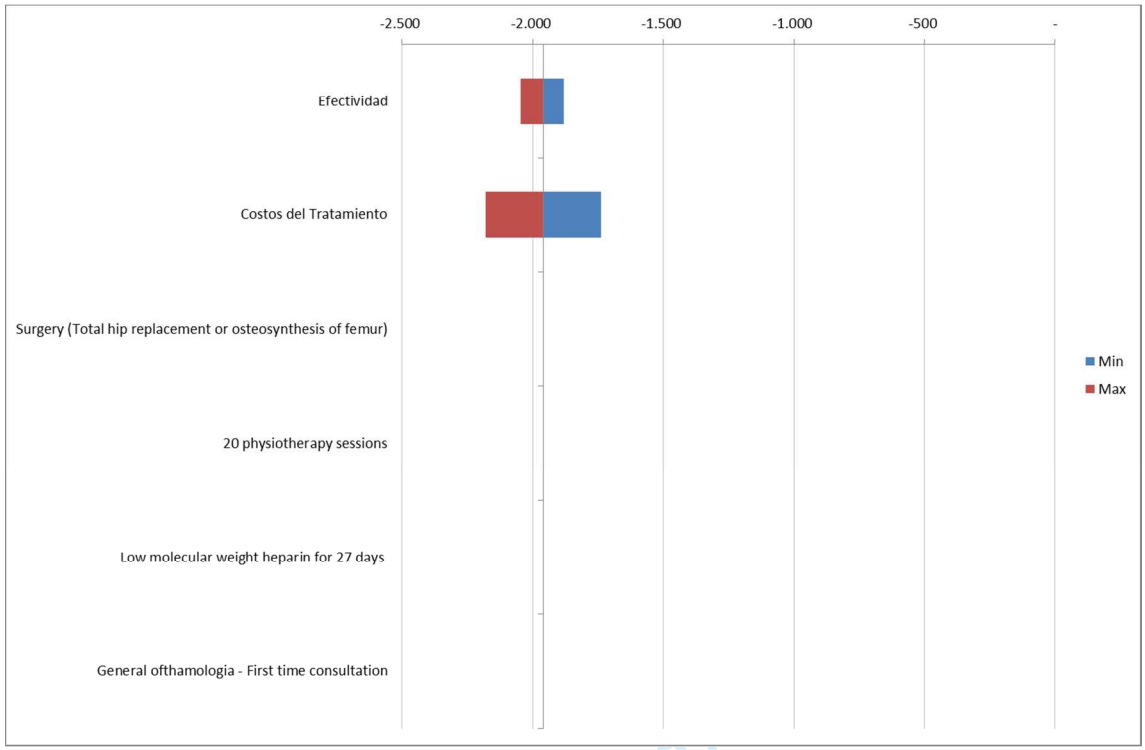
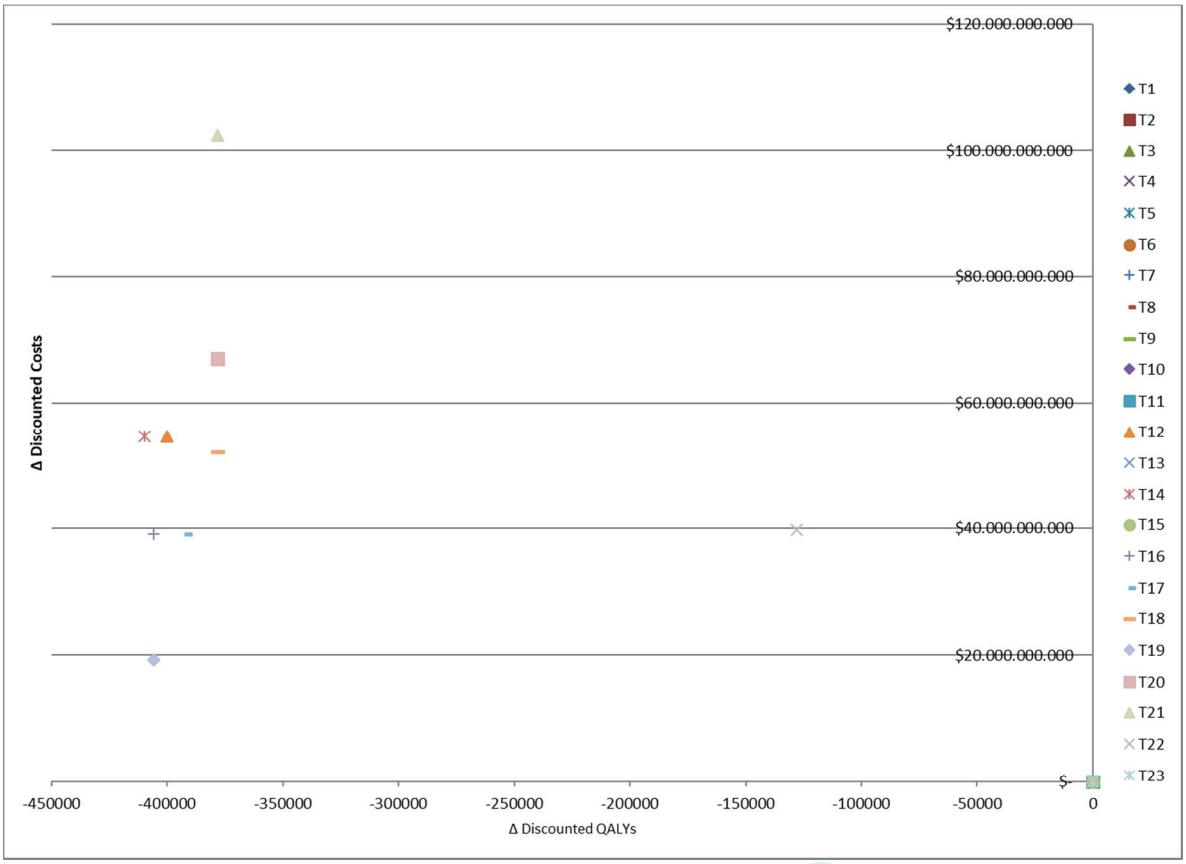


Figure 12. Cost-effectiveness plane of micro-bypass trabecular stent versus selective laser trabeculoplasty and each one of drug combinations used in Colombia for treatment of POAG, 2018.



T23: micro-bypass trabecular stent / T22: selective laser trabeculoplasty

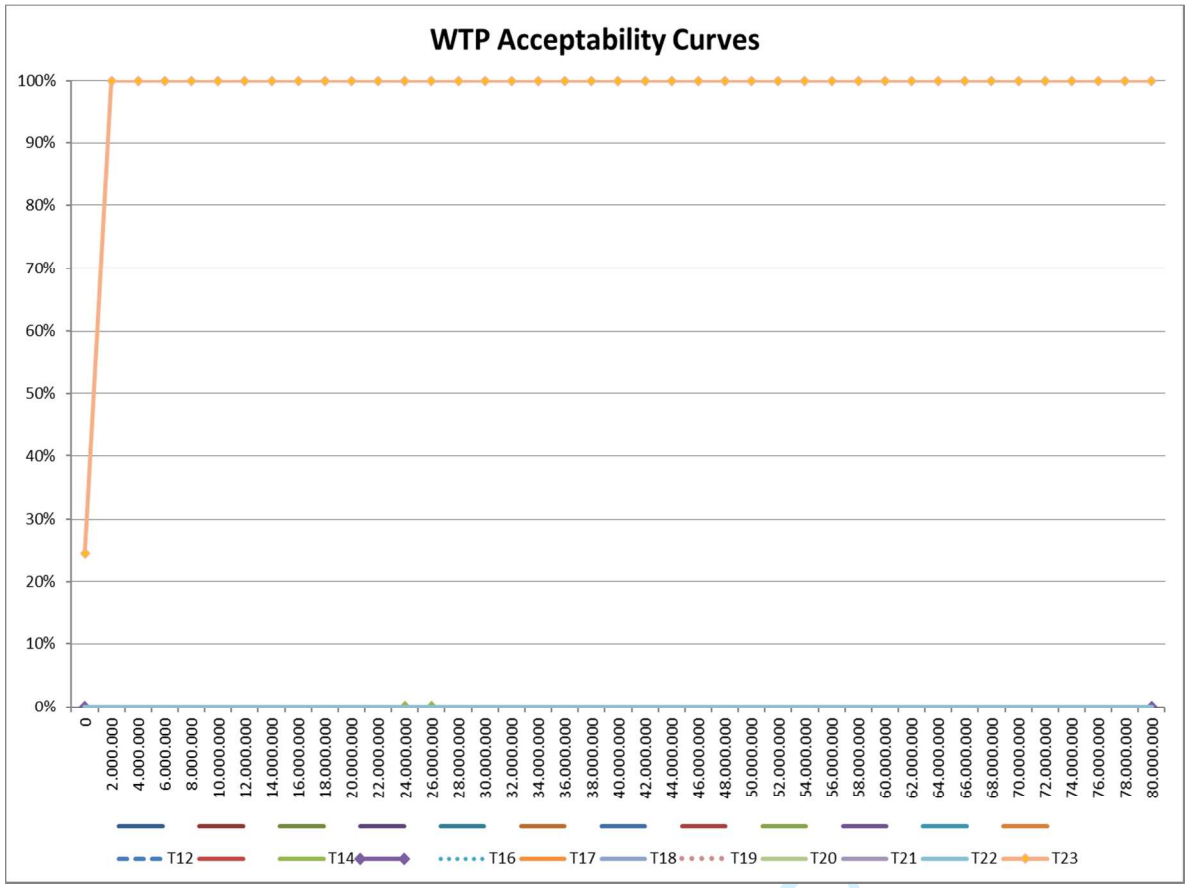
T21: travoprost + timolol + dorzolamide / T20: latanoprost + timolol + dorzolamide

T19: brimonidina + timolol + dorzolamide / T12: travaprost + timolol

T14: travaprost + timolol (Bak Free) / T16: timolol + brinzolamide

T17: timolol + brimonidine / T18: brinzolamide + brimonidine

Figure 13. Willingness-to-pay curves of the micro-bypass trabecular stent versus selective laser trabeculoplasty and each one of drug combinations used in Colombia for treatment of POAG, 2018.



T23: micro-bypass trabecular stent / T22: selective laser trabeculoplasty

T21: travoprost + timolol + dorzolamide / T20: latanoprost + timolol + dorzolamide

T19: brimonidina + timolol + dorzolamide / T12: travaprost + timolol

T14: travaprost + timolol (Bak Free) / T16: timolol + brinzolamide

T17: timolol + brimonidine / T18: brinzolamide + brimonidine

Table 1. Weighted costs of drugs for ocular hypertension treatment, according to information from SISMED database in Colombia, during 2017.

Medicine	Annual weighted mean cost (USD)
Latanoprost	$ 258.57
Travoprost	$ 385.45
Bimatroprost	$ 332.13
Tafluprost	$ 184.84
Timolol	$ 28.15
Betaxolol	$ 280.30
Brimonidine	$ 356.59
Dorzolamide	$ 232.74
Brinzolamide	$ 316.43
Pilocarpine	$ 67.64
Latanoprost + Timolol	$ 81.19
Travaprost + Timolol	$ 406.90
Bimatoprost + Timolol	$ 162.00
Travaprost + Timolol (Bak Free)	$ 406.90
Dorzolamide + Timolol	$ 191.92
Brinzolamide + Timolol	$ 350.53
Brimonidine + Timolol	$ 350.53
Brinzolamide + Brimonidine	$ 397.94
Dorzolamide + Brimonidine + Timolol	$ 279.54
Enoxaparin (27 days)	$ 58.45

Table 2. Prevalence of glaucoma in Colombia according to age groups [8].

Age group	Prevalence of glaucoma
40 – 44 years	0.07 %
45 – 49 years	0.12 %
50 – 54 years	0.20 %
55 – 59 years	0.30 %
60 – 64 years	0.47 %
65 – 69 years	0.65 %
70 – 74 years	0.86 %
75 – 79 years	0.98 %
≥ 80 years	1.11 %

Table 3. Clinical efficacy (mean, minimum and maximum values) of strategies available in Colombia for glaucoma treatment.

Treatment strategy	Mean value	Minimum	Maximum	Sources
Latanoprost	32 %	27 %	37 %	[33,34]
Travoprost	33 %	28 %	38 %	[33,34]
Bimatoprost	40 %	34 %	46 %	[33,34]
Tafluprost	27 %	23 %	31 %	[34]
Timolol	48 %	41 %	55 %	[33,35]
Betaxolol	20 %	17 %	23 %	[33]
Brimonidine	24 %	20 %	28 %	[33,36]
Dorzolamide	55 %	47 %	63 %	[33,37]
Brinzolamide	52 %	44 %	60 %	[33,37]
Pilocarpine	17 %	14 %	20 %	[38]
Latanoprost + Timolol	50 %	43 %	58 %	[39,40]
Travoprost + Timolol	38 %	32 %	44 %	[51,52]
Bimatroprost + Timolol	55 %	47 %	63 %	[35,43]
Travoprost + Timolol [Bak Free]	33 %	28 %	38 %	[44]
Timolol + Dorzolamide	49 %	42 %	56 %	[45,46]

Treatment strategy	Mean value	Minimum	Maximum	Sources
Timolol + Brinzolamide	35 %	30 %	40 %	[47]
Timolol + Brimonidine	42 %	36 %	48 %	[36,48]
Brinzolamide + Brimonidine	49 %	42 %	56 %	[49,50]
Timolol + Dorzolamide + Brimonidine	35 %	30 %	40 %	[45]
Laser surgery with argon	20 %	9 %	29 %	[51,52]
iStent® + MIGS	69,1 %	58,7 %	79,5 %	[53]

Table 4. Transition probabilities between different stages of glaucoma.

Clinical stages of glaucoma	1	2	3	4	5	Unilateral blindness	Bilateral blindness
1	0.938	0.062	0.000	0.000	0.000	0.000	0.000
2	0.000	0.950	0.050	0.000	0.000	0.000	0.000
3	0.000	0.000	0.946	0.054	0.000	0.000	0.000
4	0.000	0.000	0.000	0.940	0.060	0.000	0.000
5	0.000	0.000	0.000	0.000	0.095	0.050	0.000
Unilateral blindness	0.000	0.000	0.000	0.000	0.000	0.973	0.027

Table 5. QALY in patients with glaucoma according to level of disease severity.

Severity of the disease	Stage of glaucoma	Mean QALY	Minimum	Maximum
Mild	Stage 1	0.92	0.87	0.97
Moderate	Stage 2	0.90	0.86	0.95
	Stage 3	0.90	0.86	0.95
Severe	Stage 4	0.76	0.72	0.80
	Stage 5	0.76	0.72	0.80
Unilateral blindness		0.76	0.72	0.80
Bilateral blindness		0.33	0.31	0.35

Table 6. Risk ratio (RR) of having a hip fracture in older adults with glaucoma, according to disease clinical stage [29].

Stage of glaucoma	Risk ratio (RR)
Ocular hypertension without glaucoma	1.00
1	1.25
2	1.49
3	1.49
4	1.74
5	1.74
Unilateral blindness	1.74
Bilateral blindness	1.74

Table 7. Excess mortality by hip fracture in older adults, according to time elapsed after fracture, expressed as Hazard Ratio (HR) [61].

Time since fracture	Hazard Ratio (HR)
< 1 year	2.78
1 – 3 years	1.89
4 – 7 years	2.15
≥ 8 years	1.79

Table 8. Deterministic results of micro-bypass trabecular stent versus the laser selective trabeculoplasty surgery and the different combinations of drugs for ocular hypertension treatment (discount rate: 5 %).

Strategies	Discounted total cost (USD)	Incremental discounted total cost (USD)	Discounted QALYs	Incremental discounted QALYs	ICER (USD)
Micro-bypass trabecular stent + Timolol	$ 22,018,777		2,226,612		
Laser selective trabeculoplasty + Timolol + Dorzolamida	$ 35,272,096	-($ 13,253,318)	2,098,641	127,971	-($ 104)
Latanoprost + Timolol + Dorzolamide	$ 44,329,841	-($ 22,311,064)	1,848,325	378,287	-($ 59)
Bimatoprost + Timolol + Dorzolamide	$ 51,174,890	-($ 29,156,113)	1,848,325	378,287	-($ 77)
Travoprost + Timolol + Dorzolamide	$ 56,135,683	-($ 34,116,906)	1,848,325	378,287	-($ 90)
Brimonidine + Timolol + Dorzolamide	$ 28,422,312	-($ 6,403,534)	1,820,630	405,982	-($ 16)
Timolol + Travaprost	$ 40,273,428	-($ 18,254,651)	1,826,464	400,148	-($ 46)

Strategies	Discounted total cost (USD)	Incremental discounted total cost (USD)	Discounted QALYs	Incremental discounted QALYs	ICER (USD)
Timolol + Travaprost (Bak Free)	$ 40,273,420	-($ 18,254,643)	1,816,769	409,842	-($ 45)
Timolol + Brinzolamide	$ 35,028,573	-($ 13,009,796)	1,820,630	405,982	-($ 32)
Timolol + Brimonidine	$ 35,028,583	-($ 13,009,805)	1,834,325	392,286	-($ 33)
Brimonidine + Brinzolamide	$ 39,439,894	-($ 17,421,116)	1,848,325	378,287	-($ 46)

Table 9. Deterministic results of micro-bypass trabecular stent versus the laser selective trabeculoplasty surgery and the different combinations of drugs for ocular hypertension treatment (discount rate: 3,5 %).

Strategies	Discounted total cost (USD)	Incremental discounted total cost (USD)	Discounted QALYs	Incremental discounted QALYs	ICER (USD)
Micro-bypass trabecular stent + Timolol	$ 22,552,209		2,382,719		
Laser selective trabeculoplasty + Timolol + Dorzolamida	$ 38,315,651	-($ 15,763,442)	2,246,023	136,696	-($ 115)
Latanoprost + Timolol + Dorzolamide	$ 48,485,493	-($ 25,933,284)	1,983,242	399,477	-($ 65)
Bimatoprost + Timolol + Dorzolamide	$ 55,972,238	-($ 33,420,028)	1,983,242	399,477	-($ 84)
Travoprost + Timolol + Dorzolamide	$ 61,398,085	-($ 38,845,875)	1,983,242	399,477	-($ 97)
Brimonidine + Timolol + Dorzolamide	$ 31,086,696	-($ 8,534,487)	1,953,680	429,039	-($ 20)
Timolol + Travaprost	$ 44,048,806	-($ 21,496,596)	1,959,910	422,809	-($ 51)

Strategies	Discounted total cost (USD)	Incremental discounted total cost (USD)	Discounted QALYs	Incremental discounted QALYs	ICER (USD)
Timolol + Travaprost (Bak Free)	$ 44,048,796	-($ 21,496,587)	1,949,557	433,162	-($ 50)
Timolol + Brinzolamide	$ 38,312,267	-($ 15,760,057)	1,953,680	429,039	-($ 37)
Timolol + Brimonidine	$ 38,312,279	-($ 15,760,069)	1,968,303	414,416	-($ 38)
Brimonidine + Brinzolamide	$ 43,137,133	-($ 20,584,924)	1,983,242	399,477	-($ 52)

Table 10. Deterministic results of micro-bypass trabecular stent versus the laser selective trabeculoplasty surgery and the different combinations of drugs for ocular hypertension treatment (discount rate: 10 %).

Strategies	Discounted total cost (USD)	Incremental discounted total cost (USD)	Discounted QALYs	Incremental discounted QALYs	ICER (USD)
Micro-bypass trabecular stent + Timolol	$ 20,929,951		2,057,194		
Laser selective trabeculoplasty + Timolol + Dorzolamida	$ 28,238,466	-($ 7,308,515)	1,938,692	118,502	-($ 62)
Latanoprost + Timolol + Dorzolamide	$ 34,716,334	-($ 13,786,383)	1,701,904	355,290	-($ 39)
Bimatoprost + Timolol + Dorzolamide	$ 40,076,914	-($ 19,146,963)	1,701,904	355,290	-($ 54)
Travoprost + Timolol + Dorzolamide	$ 43,961,871	-($ 23,031,920)	1,701,904	355,290	-($ 65)
Brimonidine + Timolol + Dorzolamide	$ 22,258,637	-($ 1,328,686)	1,676,235	380,959	-($ 3)
Timolol + Travaprost	$ 31,539,630	-($ 10,609,679)	1,681,639	375,555	-($ 28)

Strategies	Discounted total cost (USD)	Incremental discounted total cost (USD)	Discounted QALYs	Incremental discounted QALYs	ICER (USD)
Timolol + Travaprost (Bak Free)	$ 31,539,626	-($ 10,609,675)	1,672,660	384,534	-($ 28)
Timolol + Brinzolamide	$ 27,432,215	-($ 6,502,264)	1,676,235	380,959	-($ 17)
Timolol + Brimonidine	$ 27,432,220	-($ 6,502,269)	1,688,925	368,269	-($ 18)
Brimonidine + Brinzolamide	$ 30,886,859	-($ 9,956,908)	1,701,904	355,290	-($ 28)

Table 11. One-way sensitive analysis of micro-bypass trabecular stent versus the laser selective trabeculoplasty surgery and the different drugs combinations for ocular hypertension treatment, adjusted by minimum and maximum effectiveness.

Strategies	Mean effectiveness	ICER of the base case (USD)	Minimum effectiveness	ICER (USD)	Maximum effectiveness	ICER (USD)
Micro-bypass trabecular stent + Timolol	69.1%		58.7%		79.5%	
Laser selective trabeculoplasty + Timolol + Dorzolamida	24.5%	-$ 104	20.8%	-$ 96	29.0%	-$ 115
Latanoprost + Timolol + Dorzolamide	24.5%	-$ 59	20.8%	-$ 57	28.2%	-$ 61
Bimatoprost + Timolol + Dorzolamide	24.5%	-$ 77	20.8%	-$ 87	28.2%	-$ 94
Travoprost + Timolol + Dorzolamide	24.5%	-$ 90	20.8%	-$ 87	28.2%	-$ 94
Brimonidine + Timolol + Dorzolamide	17.5%	-$ 16	14.9%	-$ 15	20.1%	-$ 16
Timolol + Travaprost	19.0%	-$ 46	16.2%	-$ 44	21.9%	-$ 47

Strategies	Mean effectiveness	ICER of the base case (USD)	Minimum effectiveness	ICER (USD)	Maximum effectiveness	ICER (USD)
Timolol + Travaprost (Bak Free)	16.5%	-$ 45	14.0%	-$ 44	19.0%	-$ 46
Timolol + Brinzolamide	17.5%	-$ 32	14.9%	-$ 31	20.1%	-$ 33
Timolol + Brimonidine	21.0%	-$ 33	17.9%	-$ 32	24.2%	-$ 34
Brimonidine + Brinzolamide	24.5%	-$ 46	20.8%	-$ 44	28.2%	-$ 48

Table 12. One-way sensitive analysis of micro-bypass trabecular stent versus the laser selective trabeculoplasty surgery and the different drugs combinations for ocular hypertension treatment, adjusted by minimum and maximum costs.

Strategies	Mean cost	ICER of the base case (USD)	Minimum cost	ICER (USD)	Maximum cost	ICER (USD)
Micro-bypass trabecular stent + Timolol	$ 4.722.759		$ 4.250.483		$ 5.195.035	
Laser selective trabeculoplasty + Timolol + Dorzolamida	$ 1.823.019	-$ 104	$ 1.640.717	-$ 64	$ 2.005.321	-$ 143
Latanoprost + Timolol + Dorzolamide	$ 1.501.630	-$ 59	$ 1.351.467	-$ 48	$ 1.651.793	-$ 70
Bimatoprost + Timolol + Dorzolamide	$ 1.746.832	-$ 77	$ 1.572.149	-$ 76	$ 1.921.516	-$ 104
Travoprost + Timolol + Dorzolamide	$ 1.924.537	-$ 90	$ 1.732.083	-$ 76	$ 2.116.991	-$ 104
Brimonidine + Timolol + Dorzolamide	$ 931.795	-$ 16	$ 838.615	-$ 9	$ 1.024.974	-$ 22
Timolol + Travaprost	$ 1.356.323	-$ 46	$ 1.220.691	-$ 36	$ 1.491.955	-$ 55

Strategies	Mean cost	ICER of the base case (USD)	Minimum cost	ICER (USD)	Maximum cost	ICER (USD)
Timolol + Travaprost (Bak Free)	$ 1.356.323	-$ 45	$ 1.220.691	-$ 35	$ 1.491.955	-$ 54
Timolol + Brinzolamide	$ 1.168.443	-$ 32	$ 1.051.599	-$ 24	$ 1.285.287	-$ 40
Timolol + Brimonidine	$ 1.168.443	-$ 33	$ 1.051.599	-$ 25	$ 1.285.287	-$ 41
Brimonidine + Brinzolamide	$ 1.326.464	-$ 46	$ 1.193.817	-$ 36	$ 1.459.110	-$ 56