

# Cost-Utility of Prostaglandin Analogues Compared to Beta Blockers as First-Line Medication for Treating Primary Open Angle Glaucoma in Ghana

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## Abstract

Ghana ranks among the countries most affected by glaucoma in the world. It is estimated that 700,000 people in Ghana are affected by glaucoma, out of which 60,000 people are already blind. In recent years, there has been a growing concern that anti-glaucoma medications listed on the country's health insurance medicines list are not adequate to manage the disease. This has led to calls from different stakeholders for prostaglandin analogues to be added to the medicines list. However, the cost-effectiveness of this medication is yet to be established. The objective of this study, therefore, was to establish the cost-effectiveness of prostaglandin analogues as first-line medication for treating primary open angle glaucoma in Ghana. A Markov Model was constructed to assess the life-time cost-effectiveness of treating a hypothetical cohort of one thousand 55-year-old POAG patients with prostaglandin analogues compared to beta blockers. The effect of parameter uncertainty on cost-effectiveness was explored through one-way, two-way, and probabilistic sensitivity analyses. Compared to beta blockers, prostaglandin analogues resulted in an incremental cost-effectiveness ratio (ICER) of USD 11,600; based on an estimated incremental gain of 105 quality-adjusted life years (QALYs), at an additional cost of USD 1,222,400. The ICER was not sensitive to the age of the cohort, the cost of prostaglandin analogues, or the probability of developing asthma. However, the ICER was sensitive to the age of the cohort and the cost of prostaglandin analogues when varied simultaneously. Given the existing evidence, prostaglandin analogue is not a cost-effective alternative to beta blockers as a first-line treatment for POAG in Ghana. The study, however, shows that further research to reduce decision uncertainty would be necessary if expected cost of research does not exceed USD 131 billion.

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## Keywords

Glaucoma, Ghana, Prostaglandin Analogue, Beta Blocker, ICER, Cost-Effectiveness

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## 1. Introduction

Ghana ranks among the countries most affected by glaucoma in the world [1] [2]. A recent estimate of the number of people affected by glaucoma worldwide suggested that, by 2020 there will be approximately 80 million people living with the disease, of which 11 million will be bilaterally blind [3]. In Ghana, glaucoma is estimated to account for approximately 21% of all cases of blindness [4]. It is estimated that 700,000 people in Ghana are affected by glaucoma, out of which 60,000 people are already blind [5]. Studies on incidence of glaucoma in Ghana, and Africa in general, are hard to find. Cook [6] estimated the annual incidence of glaucoma in Africa at 0.04% (*i.e.* 400 new cases for every 1 million population). Thus, considering Ghana's population of 27.41 million, the annual incidence of glaucoma can be estimated to be 10,964 per year. Glaucoma, with the resulting blindness, is a burden not only to patients, but to the entire society. To patients, the burden takes the form of pain and loss of function. It is also a burden to society in terms of resources used for treatment of patients, and productivity loss due to permanent disability associated with the disease.

"Glaucoma is a group of disorders, principally optic neuropathy resulting from cupping and atrophy of the optic nerve head leading to visual loss and blindness" [7]. Glaucoma is often associated with increased intraocular pressure (IOP) in the eye [8]. The higher the IOP, the greater the risk of visual loss [8]. IOP is measured in millimetres of mercury (mmHg). In anti-glaucoma therapy, an IOP between 19 mmHg and 22 mmHg is considered to be the safest for patients, although there is no single IOP level that is safe for every patient [7] [9]. Diagnostically, visual field loss is the most specific sign of glaucoma [7] [10]. The visual field is the portion of an individual's surroundings that can be seen at any given point in time [11]. Visual field is measured in decibels (dB) [12] [13]. Lower dB values represent lower retinal sensitivity, while higher dB values represent higher retinal sensitivity [13]. There are various types of glaucoma, but the commonest in Ghana is Primary Open Angle Glaucoma (POAG) [8]. Blindness from glaucoma is irreversible; treatment for glaucoma is, therefore, meant to reduce the risk of progression [14]. IOP is an important modifiable risk factor for glaucoma [15]. It has been proven that lowering IOP reduces progression of visual field loss in glaucoma [14] [15].

The main interventions for treating glaucoma are medications, laser therapy, and surgery [15]. The aim of glaucoma treatment, often, is to achieve a pressure reduction of at least 30% from the initial IOP [9]. There are five main classes of anti-glaucoma medications: prostaglandin analogues, beta blockers, carbonic

anhydrase inhibitors, sympathomimetics and miotics [16]. Ghana adopted a social health insurance system in 2003. The National Health Insurance Scheme (NHIS) was established by the National Health Insurance Act, 2003 (Act 650) [17]. The act also established the National Health Insurance Authority (NHIA), which regulates all health insurance schemes in the country [18]. As part of its mandate to regulate the health insurance schemes in Ghana, the NHIA has listed several anti-glaucoma medications to the health care needs of its registered clients. The NHIS medicines list includes medications extracted from all the classes of anti-glaucoma medications except prostaglandin analogues, although prostaglandin analogues are proven to be more effective [7]. This is probably because, generally, prostaglandin analogues cost more than medications from the other classes.

In recent years, there has been a growing concern that the anti-glaucoma medications listed on the country's National Health Insurance medicines list are not adequate to manage the disease. Many stakeholders have suggested that the NHIA should review the anti-glaucoma medications on the NHIS medicines list to include more medications. In their study to establish the "efficacy of NHIS-listed anti-glaucoma medications in the management of primary open-angle glaucoma in Ghana", Koffour *et al.* [7], observed that the NHIS-listed anti-glaucoma medications were not adequate in the management of POAG. The authors found that prostaglandin analogues, which were not listed by the NHIA, was more efficacious than the NHIS-listed medications. They, therefore, suggested that prostaglandin analogues, particularly latanoprost, be added to the NHIS list. A similar suggestion was made by the authors of the Ghana Eye Health System Assessment Report 2013 [1]. However, the cost-effectiveness of this medication has not yet been established. The aim of this study, therefore, was to establish the cost-effectiveness of prostaglandin analogue as a first-line medication for the management of POAG in Ghana. Currently, the main first-line anti-glaucoma medications used in Ghana are beta blockers and prostaglandin analogues (expert opinion). Thus, the study compares prostaglandin analogues to beta blockers.

Studies on glaucoma in Ghana are very scanty. Koffour *et al.* [7] established the efficacy of anti-glaucoma medications in Ghana, but did not account for their costs. Wittenborn and Rein [19] also compared the Cost-effectiveness of glaucoma interventions in Barbados and Ghana. However, the authors did not establish the cost-effectiveness between different anti-glaucoma medications. Thus, studies that establish the cost-effectiveness of anti-glaucoma medications in Ghana are almost non-existent. It is this gap that the current study seeks to fill.

The primary question that this study seeks to answer is: Is prostaglandin analogue a cost-effective first-line treatment for primary open angle glaucoma in Ghana?

Ghana is a country in West Africa. The World Bank estimates Ghana's population at 27.41 million [20]. According to the World Health Organization

(WHO), the life expectancy of a Ghanaian at birth is 63 years (*i.e.* 64 years and 62 years for females and males respectively) [21]. The World Bank classifies Ghana as a lower middle-income country [22]. The World Bank figures from 2015 estimated Ghana's gross domestic product (GDP) at USD 37.86 billion [20]. This translates into a GDP per capita of USD 1381.40. It is estimated that 24.2 percent of Ghana's population live below the poverty line, while an estimated 8.4 percent is said to be extremely poor [23]. The most recent figures available (from 2014) indicate that Ghana spends 3.6% of its GDP (approximately USD 1.36 billion) on health care [24].

Health care needs are insatiable, but the resources to meet these needs are always limited. It is, therefore, imperative to prioritize health care needs to get the most out of the limited resources. Findings from this study will, therefore, help Ghana's National Health Insurance Authority to make informed decision as to whether prostaglandin analogous can be adopted as a cost-effective first-line treatment for POAG in Ghana or not. Besides, the study will provide a relevant framework for future studies on glaucoma treatment costs and health gains, given that such studies are lacking in Ghana.

## 2. Methods and Data

### 2.1. Markov Model

A Markov model was developed to ascertain the cost-effectiveness of treating a hypothetical cohort of one thousand 55-year-old glaucoma patients until 80 years or death. The cohort entered the model at 55 years, because the mean age of POAG patients in Ghana was estimated to be 55 years (expert opinion). A Markov model is a mathematical method for quantifying the costs and health consequences of a disease as a patient progress through various disease stages over time. It is therefore useful when dealing with a chronic condition like glaucoma. "Glaucoma is a progressive disease where a patient's sight can deteriorate and never recover" [16]. The model is, therefore, a Markov model where patients cannot go back to previous health states. Data on intervention effectiveness and transition probabilities were taken from literature. Cost data were obtained mainly from Ghana's National Health Insurance Scheme (NHIS) medicines list for 2016 and the recently revised Ghana Diagnostic-related group (G-DRG) tariff lists. Costs of treatments not covered by the NHIS were estimated as the average of retail prices quoted by some leading pharmaceutical companies in Ghana.

The Hodapp, Parrish and Anderson classification, as adapted by the National Collaborating Centre for Acute Care (UK) [16] was used to define the POAG stages. The Hodapp, Parrish and Anderson classification classifies glaucoma based on severity of visual field defect. This staging system was adopted because it allows for utility values associated with different severity levels of POAG already present in literature [16]. Compared to the original staging system, the National Collaborating Centre for Acute Care (UK) collapsed the last two stages

(severe POAG and blindness), on the grounds that there was an overlap of their definitions and a lack of data of progression in the absence of treatment from severe POAG to blindness [16]. The staging classification of POAG used in the study is presented in **Table 1**.

## 2.2. The Model Structure

Five health states were used in the model, namely, early POAG, moderate POAG, advanced POAG, severe visual impairment, and death. I assumed that the cohort entered the model at early POAG stage. During each cycle, a patient may either remain in the early POAG stage, progress to moderate POAG stage, or die. Similarly, a patient at moderate POAG stage may remain in the stage, progress to advanced POAG stage or die. A patient who begins a cycle at the advanced POAG stage may also progress to severe visual impairment, remain in the advanced POAG stage, or die. Finally, a patient with severe visual impairment may remain in that stage or die during a cycle. The structure of the Markov model is presented in **Figure 1**.

The cycle length was set at 2 months as this was thought to be the minimum time after which a change in treatment could occur (expert opinion). All the probabilities, costs and health utilities were, therefore, converted to reflect the two-month values. The conversion of yearly probabilities to two-month probabilities involved two steps. First, the annual probability was converted to two-month rate using Equation (1).

$$r = -[\ln(1 - p)]/t \quad (1)$$

where  $r$  = rate,  $p$  = probability,  $t$  = period of interest

The two-month rate was then converted to two-month probability by rearranging Equation (1).

$$p = 1 - \exp^{(-rt)} \quad (2)$$

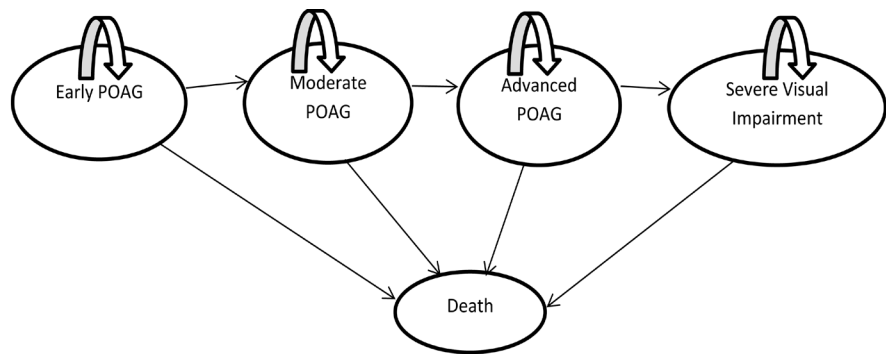
## 2.3. Baseline Probability of Progression

A search was conducted for studies reporting the probability for progression from one POAG stage to the next. Specifically, the search was to identify studies that reported the probability of progression from Early to Moderate POAG in

**Table 1.** Staging Classification for POAG.

POAG Stage	Defect Score Interval (in decibels)
No POAG	No visual field defect
Early	-0.01 to -6.00 dB
Moderate	-6.01 to -12.00 dB
Advanced	-12.01 to -20.00 dB
Severe Visual Impairment	-20.01dB or worse

Source: (National Collaborating Centre for Acute Care (UK), 2009).



**Figure 1.** Structure of the markov model.

treated and untreated patients, from Moderate to Advanced POAG in treated and untreated patients, and from Advanced POAG to Severe Visual Impairment in treated and untreated patients. Only studies using a definite staging system were included. The search yielded two relevant results. Using randomized controlled trials (RCTs), Burr *et al.* [25] estimated the progression rates of mild, moderate, and severe POAG stages based on visual field mean defect. These stages correspond to the National Collaborating Centre for Acute Care (UK) [16] definitions of early, moderate and advanced POAG, being employed in this study. The National Collaborating Centre for Acute Care (UK) adopted Burr's progression rates, and projected the progression rate for severe visual impairment, which was missing in Burr's study. The annual progression probabilities, as presented by the National Collaborating Centre for Acute Care (UK) [16], were employed in this study, because they cover all the relevant POAG stages. The annual probabilities were converted to two-month probabilities using Equations (1) and Equation (2) as shown in **Table 2**.

#### 2.4. Treatment Effects

Patients diagnosed with POAG could be treated either with beta-blockers or a prostaglandin analogues as first-line treatment. The main treatment effect considered was a change in risk of progression to the next POAG stages. However, the most commonly reported treatment outcome in literature is the change in intraocular pressure (IOP). Data on reduction in IOP from baseline due to each treatment was derived from the National Collaborating Centre for Acute Care (UK) [16] (**Appendix 1**). This was done because the data presented by the National Collaborating Centre for Acute Care was based on rigorous search for systematic reviews of clinical effectiveness of treatments in POAG patients.

Conversion of a change in IOP to a change in probability of progression involved two steps. First the change in IOP (*i.e.* mean reduction in IOP) associated with each intervention was multiplied by the percentage reduction in progression per 1 mmHg reduction in IOP to obtain the effectiveness of the intervention using Equation (3). Percentage reduction in progression per 1 mmHg reduction in IOP was taken from Leske *et al.* [26], who found that a 1 mmHg reduction in IOP is associated with 8% decrease in progression from one POAG

**Table 2.** Baseline probability of progression in POAG patients.

Transition	Annual Probability in Untreated Patients	Two-Months Probability in Untreated Patients	Annual Probability in Treated Patients	Two-Months Probability in Treated Patients
Early to Moderate POAG	0.25	0.048	0.20	0.037
Moderate to Advanced POAG	0.11	0.019	0.07	0.012
Advanced POAG to Severe Visual Impairment	0.10	0.018	0.06	0.01

Source: (National Collaborating Centre for Acute Care (UK), 2009)

stage to the next.

$$Eff_i = \Delta IOP_i * \Delta P \quad (3)$$

where:

$Eff_i$  = Effectiveness of intervention  $i$

$\Delta IOP_i$  = change in IOP associated with intervention  $i$

$\Delta P$  = percentage change in progression associated with 1 mmHg change in IOP

$i$  = beta blockers, prostaglandin analogues

Subsequently, the baseline probability of progression without treatment was adjusted by the effectiveness of the respective treatment to obtain the probability of progression after treatment using Equation (4).

$$TP_i = BPu * (1 - Eff_i) \quad (4)$$

where:

$TP_i$  = Transition probability associated with intervention  $i$

$BPu$  = Baseline transition probability in untreated patients

A ratio between the probability of progression associated with prostaglandin analogues and that of beta blockers gave a relative risk of 0.843. The probabilities are shown in **Table 3**.

The probabilities in **Table 3** were used only in early POAG. Once a patient progressed from early POAG, the baseline probability in treated patients for the respective stage was used (**Table 2**). The transition probabilities for nonspecific treatments were used, because after progression any new treatment could be introduced.

Some treatments for glaucoma could cause adverse events. "Nevertheless, not all of them result in important increased costs or reduced quality of life" [16]. Asthma (associated with beta blockers) was the only complication considered in the model, because, as far as medical treatment is concerned, asthma is the only known complication with a considerable impact on costs and quality of life [16]. Probability of developing asthma after use of beta blockers was taken from a prospective cohort study [27]. The authors compared the difference in respiratory disease in 2645 patients treated with beta blockers to a control group of 9094 patients who were not exposed to beta blockers. After 12 months, it was

**Table 3.** Probability of Progression after Treatment.

Intervention	Annual Probability in Untreated Patients	Overall Annual Progression Reduction	Annual Probability of Progression	Two-Months Probability of Progression	Relative Risk
Beta Blockers	0.25	0.23	0.193	0.0351	-
Prostaglandin Analogues	0.25	0.34	0.165	0.0296	0.843 <sup>a</sup>

a 0.0296/0.0351.

observed that patients who were treated with beta blockers were 3.3% more likely to develop reversible airways obstruction than those who were not exposed. This translates into a two-month probability of 0.6%. The study, however, showed that the risk of respiratory problems was no longer significant after the first year of exposure. Hence the probability of developing asthma was used in the model only within the first year.

Probabilities of death were obtained from 2013 life table for Ghana as shown by WHO [28] (see **Appendix 2**). Life expectancy in patients with POAG was assumed to be the same as the general population in Ghana. Similarly, life expectancy in POAG patients who develop asthma due to the use of beta blockers was assumed to be the same as that of the general population in Ghana. The key parameters used in the model are summarized in **Table 4**.

## 2.5. Treatment Outcomes

Health gain was measured in terms of quality-adjusted life-years (QALYs). Health utilities for the health states used in the model were obtained from literature. Except for asthma, all adverse events were assumed to be negligible in terms of quality of life since, according to the National Collaborating Centre for Acute Care (UK) [16], they could be promptly treated. Disutility due to asthma was estimated from quality of life measures in treated asthma patients as presented in literature.

A search was conducted for studies reporting health utilities for patients at the various stages of POAG. The search yielded three results [16] [29] [30]. van Gestel *et al.* [29] could not be used because the authors did not employ the staging classification being used in this study. Similarly, Béchetuille *et al.* [30] could not be used, because the authors did not report the overall health related quality of life (HRQoL) for the stages; rather HRQoL was reported per different health domains. The HRQoL reported by National Collaborating Centre for Acute Care (UK) [16], which followed the same staging classification as adopted in this study, were therefore used. The National Collaborating Centre for Acute Care (UK) estimated the health utilities from Rein, Wirth, Johnson, and Lee [31], who applied utilities for visual acuity to each category of visual field loss using data obtained from Brown, Brown, Sharma, and Landy [32]. The original data was based on EQ-5D.



**Table 4.** Key Parameters used in the Markov Model.

Parameter	Value	Distribution
Transition probability from early POAG to moderate POAG (BB)	0.0351	Dirichlet
Probability of staying in early POAG (BB)	0.9585	Dirichlet
Transition probability from early POAG to death (BB)	0.0064	Dirichlet
Transition probability from early POAG to moderate POAG (PA)	0.0296	Dirichlet
Probability of staying in early POAG (PA)	0.964	Dirichlet
Transition probability from early POAG to death (PA)	0.0064	Dirichlet
Transition probability from moderate POAG to advanced POAG	0.012	Dirichlet
Probability of staying in moderate POAG	0.9816	Dirichlet
Transition probability from moderate POAG to death	0.0064	Dirichlet
Transition probability from advanced POAG to severe visual impairment	0.0103	Dirichlet
Probability of staying in advanced POAG	0.9834	Dirichlet
Transition probability from advanced POAG to death	0.0064	Dirichlet
Probability of staying in severe visual impairment	0.9937	Beta
Transition probability from severe visual impairment to death	0.0064	Beta
Probability of asthma (BB)	0.006	Beta
Probability of no asthma (BB)	0.994	Beta
Two-month discount rate	0.0025	-
Relative risk for prostaglandin analogues	0.8433	Lognormal
Probability of needing medication in severe visual impairment	0.1	Beta
Probability of not needing medication in severe visual impairment	0.9	Beta
Cost of treatment for early POAG patients who use beta blockers	3.77	Gamma
Cost of treatment for early POAG patients who use prostaglandin analogues	51.54	Gamma
Cost of treating asthma patients	28.78	Gamma
Cost of treating moderate POAG patients	34.91	Gamma
Cost of treating advanced POAG patients	54.67	Gamma
Cost of treating patients with severe visual impairment	3.77	Gamma
Health-related quality of life for patients with early POAG	0.989	Lognormal
Health-related quality of life for patients with moderate POAG	0.944	Lognormal
Health-related quality of life for patients with advanced POAG	0.819	Lognormal
Health-related quality of life for patients with severe visual impairment	0.503	Lognormal
Health disutility due to asthma	0.14	Lognormal

BB = Beta blockers PA = Prostaglandin analogues.

A search for quality of life measures in treated asthma patients retrieved two studies [33] [34], which respectively reported the health utility in treated asthma patients as 0.84 and 0.86. Both studies used EQ-5D. However, I opted for Chen

*et al.* [34], since it is more current. I therefore assumed that treated asthma symptoms reduce quality of life by 0.14 over one year. Health utilities used in the model are summarized in **Table 4**.

For each strategy, the expected health benefits were calculated by estimating the health effects for each POAG stage and then multiplying them by the proportion of patients who would be in that stage as determined by the strategy taken. The expected health benefit per the cohort in each cycle was calculated using Equation (5).

$$\text{Expected Health Benefit} = \sum(Q_i \times P_i) \quad (5)$$

where:

$Q_i$  = health utility of stage  $i$

$P_i$  = proportion of patients in the stage  $i$

$i$  = early POAG, moderate POAG, advanced POAG, severe visual impairment

The proportion of patients in each POAG stage depends on the magnitude of the progression reduction of the treatment and on the proportion of patients still alive per the mortality rate for the general population of Ghana.

## 2.6. Costs

The study adopted the health care provider's perspective. This was because the study was meant to inform the NHIA of Ghana, whose responsibility is limited to the costs incurred by the health care provider in providing services to NHIS card holders. All costs used in the model were estimated using a bottom-up approach. Follow-up costs were not considered in the model. Where the primary interest is incremental cost, as is the case when comparing the introduction of a new intervention against an existing intervention, costs that remain approximately the same for each alternative being considered can be ignored [35] [36] [37]. This is because such costs will not affect the choice between the given alternatives [35] [37]. All glaucoma patients in Ghana are followed up every two months, except a few patients whose IOP levels are exceptionally too high, or who develop intolerance to treatment before their next appointment date (expert opinion). Besides, follow-up procedures are the same for all glaucoma patients in Ghana, irrespective of their level of the disease. Hence, I assumed that follow-up cost is the same for both the intervention group and the comparator group. Since my primary interest is incremental cost, I decided not to include the follow-up cost.

Costs of all medicines were obtained from Ghana's NHIS medicines list for 2016 [38], except the cost of latanoprost which was not covered by the NHIS. Cost of latanoprost was taken as an average of the retail prices quoted by some leading pharmaceutical companies in Ghana. Two versions of latanoprost are used in Ghana, namely branded latanoprost (Xalatan) and generic latanoprost. The costs of these two versions were averaged. The cost of glaucoma surgery (trabeculectomy) was also obtained from the recently revised Ghana Diagnostic-related group (G-DRG) tariff lists [39] [40]. The G-DRG offers different tariffs

for services provided at Public Primary Care Hospitals and those provided at Christian Health Association of Ghana (CHAG) Primary Care Hospitals. The cost of glaucoma surgery was, therefore, taken as the average of the tariffs for Public Primary Care Hospitals and CHAG Primary Care Hospitals respectively. For purposes of comparison, all costs were presented in United States Dollars (USD), based on Bank of Ghana exchange rates for 30th June 2016 (USD 1.00  $\approx$  GHC 3.9240). The unit costs of resources used in the model are presented in **Appendix 3**.

Costs were categorized based on the health states used in the model. Hence the cost categories include early POAG costs, moderate POAG costs, advanced POAG costs, severe visual impairment costs, and costs of adverse events. Early POAG costs are costs incurred in treating a patient diagnosed with early POAG. They are costs that arise before progression from early POAG stage. As already mentioned, the model primarily compares the first-line anti-glaucoma medications used in Ghana (*i.e.* beta blockers and prostaglandin analogues). Hence, early POAG costs are those costs directly associated with either beta blockers or prostaglandin analogues as a mono therapy.

When mono-therapy fails to significantly lower IOP, combination therapy is sought for [7]. I assumed that all patients who progressed beyond early POAG were given combination therapies. Koffuor *et al.* [7] observed that, in Ghana, a POAG patient could be given up to four-medication combination therapies, depending on the severity of the disease and patients' tolerance to medication. However, the number of patients on four-medication combination therapy, as reported in their study, was almost insignificant. Therefore, I assumed that patients at moderate and advanced POAG stages are put on two-medication and three-medication combination therapies respectively. Besides, at both moderate and advanced POAG stages, a patient can undergo surgery (trabeculectomy). Although some patients undergo laser trabeculoplasty, the practice is not common in Ghana (expert opinion). This option was, therefore, ignored. It was assumed (based on expert opinion) that 10% of patients with severe visual impairment are given timolol to ease the pain in the affected eye; the remaining is not given further treatment.

All adverse events, except asthma, were assumed to be negligible in terms of costs. The cost of treating asthma was estimated based on the Standard Treatment Guidelines of Ghana [8]. I assumed that no additional follow-up cost was associated with the change in treatment due to asthma.

The key cost inputs used in the model are summarized in **Table 4**. For each strategy, the expected cost per the cohort in each cycle was calculated using Equation (6).

$$\text{Expected cost} = \sum (C_i \times P_i) \quad (6)$$

where:

$C_i$  = cost of stage  $i$

$P_i$  = proportion of patients in the stage  $i$

$i$  = early POAG, moderate POAG, advanced POAG, severe visual impairment

## 2.7. Analyses

The cost-effectiveness analysis was conducted using Microsoft Excel 2016. All future costs and QALYs were discounted at the rate of 3 percent per annum in line with Global Burden of Disease [41], using Equation (7).

$$PV = \frac{FV}{(1+r)^n} \quad (7)$$

where:

$PV$  = Present value

$FV$  = Future value

$r$  = Discount rate

$n$  = Number of periods under consideration

Costs and health outcomes were corrected for continuity. This was done by dividing the costs and health outcomes of the first and the last cycles by 2, as shown in Equation (8).

$$A = 1/2 + 1 + 1 + 1 + \dots + 1 + 1 + 1 + 1/2 \quad (8)$$

where  $A$  = total cost, total health effect.

The overall lifetime expected health benefit of each intervention is given by the sum of health benefits calculated for all the cycles. Since each cycle represented 2 months, the overall lifetime expected health benefit was divided by 6 to get the overall lifetime QALYs. The incremental QALY ( $\Delta E$ ) associated with prostaglandin analogues was calculated as the difference between the expected QALY gained with prostaglandin analogues and the expected QALY gained with the comparator (beta blockers).

Similarly, the overall lifetime expected cost of each intervention is given by the sum of costs calculated for all the cycles. The incremental cost ( $\Delta C$ ) associated with prostaglandin analogues was calculated as the difference between the expected cost with prostaglandin analogues and the expected cost with beta blockers.

## 2.8. Incremental Cost-Effectiveness Ratio (ICER)

The result of cost-utility analysis was expressed as incremental cost-effectiveness ratio (ICER), *i.e.* the ratio of incremental costs ( $\Delta C$ ) to incremental effects ( $\Delta E$ ) brought about by prostaglandin analogues compared to beta blockers. Thus, the numerator of the ICER is the difference in cost between patients in the intervention group and those in the comparator group, while the denominator is the difference in health outcomes (QALYs) between patients in the intervention group and those in the comparator group. The ICER is defined by Equation (9).

$$ICER = \Delta C / \Delta E \quad (9)$$

where:

$\Delta C$  = incremental cost

$\Delta E$  = incremental effect

To determine whether, or not, prostaglandin analogues was cost-effective, the resulting ICER was compared to the society's willingness-to-pay threshold ( $\lambda$ ). Prostaglandin analogue would be cost-effective only if the ICER was less than the willingness-to-pay threshold (*i.e.*  $\Delta C/\Delta E < \lambda$ ).

The willingness-to-pay threshold for Ghana was set to be equal to three times the country's GDP per capita. Ghana's GDP per capita for 2015, according to the World Bank [20] was USD 1381.40. Hence, the willingness-to-pay threshold equals USD 4144.20 ( $\approx$  USD 4,100).

## 2.9. Sensitivity Analyses

Sensitivity analyses were performed to assess the robustness of the model results against the imprecision in the model parameters. Almost all parameters used in the model were estimates; there is uncertainty surrounding their true values. The purpose of sensitivity analyses was to capture this uncertainty in the model. One-way, two-way, and probabilistic sensitivity analyses were performed.

One-way sensitivity analysis was performed on probability of developing asthma, age of the cohort, and cost of latanoprost. I found that costs and QALYs in the comparator could be significantly influenced by asthma. For this reason, I conducted a one-way sensitivity analysis on the probability of developing asthma. In the base-case model, the annual probability of developing asthma in patients using beta blockers was set to be 3.3%. However, in the sensitivity analysis the probability was varied between 0 and 6%. Age largely influences longevity. The age at which the cohort entered the model would, therefore, determine how long the patients would live to benefit from the intervention. If the cohort dies out too quickly, the full effect of the intervention may not be realized. One-way sensitivity analysis was, therefore, performed on the age of the cohort to determine how varying the age of the cohort would affect the results. In the base-case analysis, the age of the cohort was set at 55 years. However, in the sensitivity analysis, the age of the cohort was varied between 30 years and 75 years. I also performed one-way sensitivity analysis on the cost of prostaglandin analogues (*i.e.* latanoprost). This was because the disparity between the cost of generic latanoprost and branded latanoprost (Xalatan) was very wide. In the base-case model, the cost per bottle of prostaglandin analogues was estimated at USD 25.77 (reflecting the mean cost of generic latanoprost and Xalatan). In the sensitivity analysis, however, the cost was varied from USD 13.00 (corresponding to the cost per bottle of generic latanoprost) to USD 39.00 (corresponding to the cost per bottle of Xalatan). A two-way sensitivity analysis was also performed to ascertain the combining effect of the age of the cohort and the cost of prostaglandin analogues on the results.

In the probabilistic sensitivity analysis (PSA), probability distributions were assigned to each model parameter where there was some degree of parameter variability. The main results were then re-calculated 1000 times; each time all the

model parameters were set simultaneously, selecting from the respective parameter distribution at random. The decision uncertainty was represented by plotting a cost-effectiveness plane, a cost-effectiveness acceptability curve (CEAC), and a cost-effectiveness acceptability frontier (CEAF).

### 2.10. Expected Value of Perfect Information (EVPI)

Considering the uncertainty surrounding the results, it became imperative to establish whether it was worthy, or not, to gather more evidence. The EVPI was estimated directly from the results of the PSA. The EVPI is the difference between the expected net benefit with perfect information and that of current information. The EVPI was estimated using the following steps. First, the average overall net monetary benefits (NMBs) from the 1000 simulations for each intervention were calculated. With current information, the optimal decision is the intervention with the maximum expected net benefit. Afterwards, the maximum of the net benefits between the two interventions for each simulation were chosen, summed up and averaged to get the expected net benefit of a decision with perfect information. The EVPI was then estimated as the difference between the expected net benefit with perfect information and the expected net benefit with current information. The EVPI thus estimated was for a single individual.

To decide whether to invest in additional research or not, the size of the population that is expected to benefit from the new intervention and the relevant time horizon of the new intervention must be taken into account [42]. The incidence of glaucoma in Ghana was estimated at 10,964 per annum. It was assumed that 192,000 people currently living with glaucoma in Ghana (approximately 27.5% of the estimated prevalence of 700000) would also be eligible for the new intervention. It was further assumed that prostaglandin analogues would be useful for 10 years. Population EVPI was calculated as the product of the individual EVPI and the total number of people who are expected to benefit from the intervention (Equation (10)). Incidence associated with future years was discounted at the rate of 3%.

$$\text{Population EVPI} = \text{EVPI} \cdot \sum_{t=1,2,\dots,T} I_t / (1+r)^t \quad (10)$$

where:

$T$  = expected lifetime of the new intervention

$I_t$  = estimated incidence of the disease over the period

$r$  = discount rate

Population EVPI estimates were calculated over a cost-effectiveness threshold range of USD 0 to USD 60,100 per QALY. As a decision rule, further research is potentially cost-effective if population EVPI exceeds the expected cost of additional research at any given threshold.

## 3. Results

### 3.1. Base-Case Cost-Effectiveness Analysis Results

The expected cost of treating 1000 patient with prostaglandin analogues (USD

3,886,100) is higher compared to beta blockers (USD 2,663,700). Similarly, QALY gained from prostaglandin analogues (14,231) is higher compared to beta blockers (14,126). The incremental cost-effectiveness ratio (ICER) is USD 11,600 per QALY gained (**Table 5**).

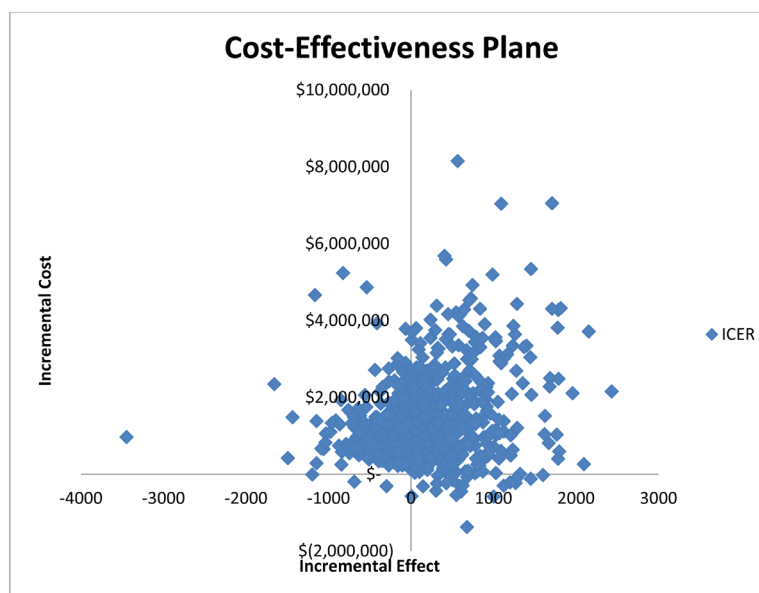
This implies that that if we choose prostaglandin analogues as first line treatment for POAG patients in Ghana instead of beta blockers, we would gain additional QALYs at an additional cost of USD 11,600 per each QALY gained. The ICER is greater than three times the GDP per capita of Ghana (USD 4,100). This implies that prostaglandin analogue is not a cost-effective first-line medication for the treatment of POAG in Ghana.

### 3.2. Sensitivity Analyses

In the one-way sensitivity analysis, the ICER was not sensitive to the probability of developing asthma after the use of beta blockers (**Appendix 4**). Similarly, the ICER was neither sensitive to the age of the cohort nor the cost of prostaglandin analogues (**Appendix 5 & Appendix 6**). In the two-way sensitivity analysis, however, the ICER was sensitive to the age of the cohort and the cost of prostaglandin analogues when varied simultaneously. When the age of the cohort was set at 41 years, and the cost of prostaglandin analogues at USD 13.00, prostaglandin analogues became cost-effective (**Appendix 7**). This implies that, generic

**Table 5.** Summary of Results.

Intervention	Cost (USD)	QALY	Incremental Cost (USD)	Incremental QALY	ICER
Beta Blockers	2,663,700	14,126	-	-	-
Prostaglandin analogues	3,886,100	14,231	1,222,400	105	11,600



**Figure 2.** Cost-effectiveness plane.

latanoprost (costing USD 13.00 per bottle) could be cost-effective for treating POAG patients 41 years old and below.

Results from the probabilistic sensitivity analysis were presented using a cost-effectiveness plane, a cost-effectiveness acceptability curve (CEAC), and a cost-effectiveness acceptability frontier (CEAF).

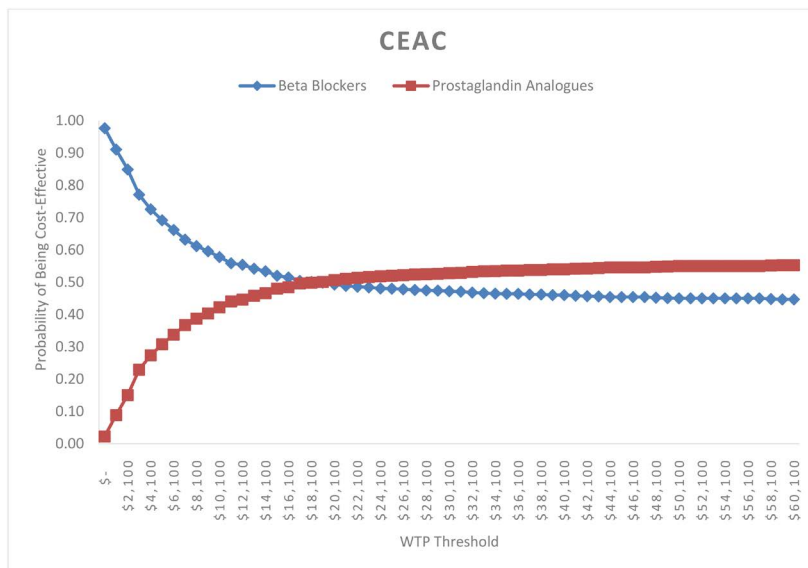
The cost-effectiveness plane (**Figure 2**) shows the spread of pairs of incremental costs ( $\Delta C$ ) and incremental effectiveness ( $\Delta E$ ) values from running 1,000 Monte Carlo simulations. The x-axis shows incremental effectiveness, while the y-axis shows incremental cost. The slope of the line joining any point on the plane to the origin is equal to the incremental cost-effectiveness ratio (ICER). A cost-effectiveness plane has four quadrants: northeast (NE), southeast (SE), southwest (SW), and northwest (NW) (Briggs *et al.*, 2006). A new intervention is said to dominate its comparator (more effective and less costly) if it is located in the SE quadrant. Conversely, a new intervention is said to be dominated by its comparator (less effective and more costly) if it is located on the NW quadrant. A new intervention is more effective and more costly if it is located in the NE quadrant, while a new intervention that is located in the SW quadrant is less effective and less costly.

In the cost-effectiveness plane, 977 (almost 98%) of the cost-effectiveness pairs are concentrated on the northeast and northwest quadrants. This suggests that prostaglandin analogue is more costly than beta blockers, although this cannot be said with 100% certainty. The locations of the ICER points on the cost-effectiveness plane, however, makes it highly uncertain to tell whether prostaglandin analogue is more effective than beta blockers: 41% fell in the northwest and southwest quadrants, while 59% fell in the northeast and southeast quadrants.

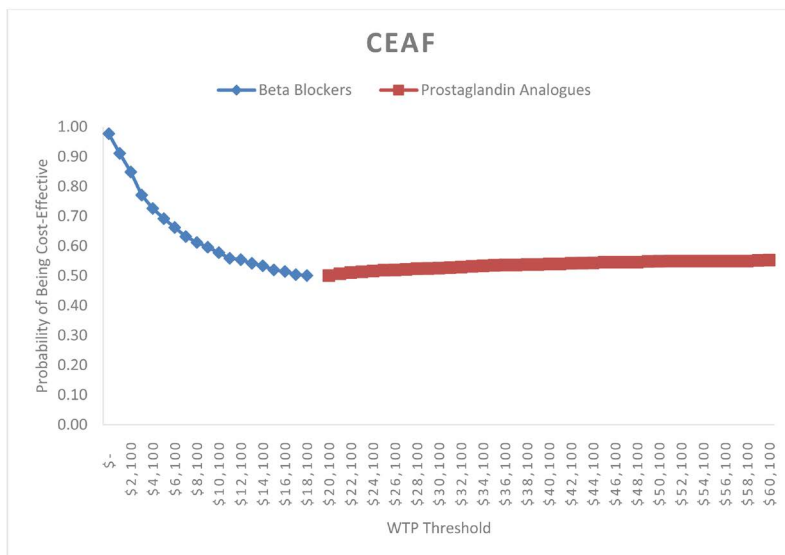
In the cost-effectiveness acceptability curve (CEAC), presented in **Figure 3**, the y-axis indicates the probability that prostaglandin analogue is cost-effective compared to beta blockers, given a range of willingness-to-pay threshold values (on the x-axis). At a willingness-to-pay threshold of USD 0 per QALY gained, the probability of prostaglandin analogues being cost-effective compared to beta blockers was 0.02. The CEAC, however, shows that the probability of prostaglandin analogues being cost-effective increases as the willingness to pay for additional QALYs increases. When the willingness-to-pay threshold increases to USD 4,100, the probability of prostaglandin analogue being cost-effective compared to beta blockers increases to 0.27. At the same willingness-to-pay threshold, the probability of beta blockers being cost-effective was 0.73. This seems to suggest that prostaglandin analogue is not cost-effective compared to beta blockers. However, this cannot be said with absolute certainty since the probability of prostaglandin analogue being cost-effective is greater than 0.

The cost-effectiveness acceptability frontier (CEAF) in **Figure 4** indicates the probability that the alternative with the highest net-benefit will be cost-effective. Hence the decision uncertainty (or error probability) is 1 minus the value of the frontier. Like the CEAC, the CEAF shows that, at the willingness to pay threshold of USD 4100, the comparator (beta blockers) is cost-effective. The proba-





**Figure 3.** Cost-Effectiveness Acceptability Curve.



**Figure 4.** Cost-Effectiveness Acceptability Frontier.

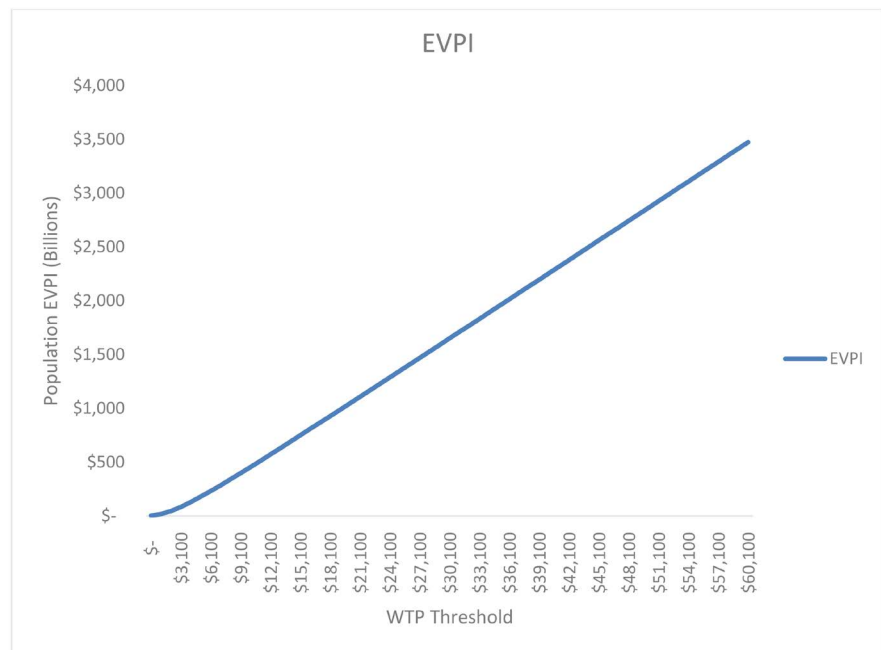
bility of beta blockers being cost-effective is 0.73 with error probability of 0.27.

### 3.3. Expected Value of Perfect Information (EVPI)

Figure 5 shows population EVPI for a range of willingness-to-pay threshold values between USD 0 and USD 60,100. Given a willingness to pay threshold of USD 4100, the population EVPI is USD 131 billion. This implies that further research would be potentially cost-effective if expected cost of further research is less than USD 131 billion. Beyond this value, further research is not worthwhile.

## 4. Discussion

There has been a growing concern in Ghana, recently, that anti-glaucoma medi-



**Figure 5.** Population EVPI.

cations listed on the country's National Health Insurance Scheme's (NHIS) medicines list are not adequate to manage glaucoma. This has led to calls from many stakeholders for prostaglandin analogues, particularly latanoprost, to be added to the NHIS medicines list. However, the cost-effectiveness of prostaglandin analogues is yet to be established. The health care system of Ghana is faced with many challenges. Perhaps the greatest challenge that the health care system faces is inadequate funding. The resource constraints of the country make it highly important to establish the cost-effectiveness of prostaglandin analogues before recommending it to the National Health Insurance Authority. This study reports an economic evaluation modelling framework to compare the cost effectiveness of prostaglandin analogues with beta blockers as first line treatment for primary open angle glaucoma in Ghana.

#### 4.1. Cost-Utility Analysis

Results from this study indicate that prostaglandin analogue is more effective, but also more costly, compared to beta blockers. The results also show that prostaglandin analogue is not a cost-effective alternative to beta blockers as a first-line medication for primary open angle glaucoma in Ghana, given the current economic situation of the country. A two-way sensitivity analysis on the age of the cohort and the cost of prostaglandin analogues (latanoprost), however, showed that generic latanoprost could be cost-effective for treating primary open angle glaucoma patients 41 years and below. This finding, especially with respect to age, seems to suggest that the full benefit of prostaglandin analogues can only be observed in the long run. Thus, even at USD 13.00 per bottle, prostaglandin analogue was not cost-effective for the cohort used in the base-case

analysis (55 years) because the cohort had a higher probability of death, and therefore died out too quickly to benefit fully from the intervention. However, it became cost-effective for a younger cohort (41 years and below), with a lower probability of death.

The probabilistic sensitivity analysis reveals some level of uncertainty surrounding the results of the cost-effectiveness analysis. Results from EVPI suggest that further evidence would be necessary to reduce decision uncertainty provided that the expected cost of further research does not exceed USD 131 billion.

## 4.2. Related Studies

There are several studies that seek to establish the cost-effectiveness of treatment interventions for glaucoma. However, studies that compare different anti-glaucoma medications are limited. In Ghana, economic evaluation studies on glaucoma treatment are very scanty. Kuffuor *et al.* [7], who established the efficacy of anti-glaucoma medications in Ghana, did not account for their costs. Wittenborn & Rein [19] also compared the cost-effectiveness of glaucoma interventions in Barbados and Ghana, but did not consider the cost-effectiveness between different anti-glaucoma medications. Thus, studies that establish the cost-effectiveness of anti-glaucoma medications in Ghana are almost non-existent. As far as I know, this is the first study that seeks to establish the cost-effectiveness between anti-glaucoma medications for treating primary open angle glaucoma in Ghana. The model reported in this study, therefore, provides a relevant framework for further studies on glaucoma treatment costs and health gains.

## 4.3. Limitations of the Study

The study has several limitations, which could have influenced the incremental cost and/or incremental QALY, and for that matter the ICER. The limitations stem mainly from the key assumptions of the model.

As far as medical treatment is concerned, the only adverse event I considered was asthma. All other adverse events were assumed to be negligible since they could be promptly treated. This assumption may have led to underestimation of costs and overestimation of QALYs under both interventions. It is, however, difficult to tell which direction this limitation would have driven the ICER. The direction of the effect would depend on the specific adverse events associated with each intervention, the reduction in QALYs due to each adverse event, and the cost involved in treating the respective events.

Besides, all post-surgery complications were assumed to be negligible. Clearly, this assumption might have led to underestimation of costs in both groups. However, the possible impact of this limitation on the ICER would depend on how many patients in each intervention group had complications after undergoing surgery.

It was further assumed that POAG patients would not need any anti-glaucoma medication after they have undergone surgery. In practice, however, some

POAG patients may have elevated IOP even after surgery, and would therefore need further medical treatment. Ignoring this probability might have led to understatement of costs in both groups.

Furthermore, I assumed no extra follow-up costs for POAG patients who developed asthma after the use of beta blockers. This assumption might have led to underestimation of costs associated with beta blockers and, hence, overestimation of the ICER.

I also assumed that no patient died from asthma that resulted from the use of beta blockers. Neglecting possible asthma-related deaths could have led to overestimation of QALYs gained under beta blockers and, therefore, underestimation of incremental QALYs, and eventually overestimation of the ICER.

Another limitation of the study stems from the assumption that there was no shift in treatment before a patient progressed from early POAG stage. In practice, patients at early POAG stage who show intolerance to beta blockers or prostaglandin analogues may be shifted to another treatment before they progress to the next stage. This assumption might, therefore, have led to underestimation of costs under both interventions.

Utility measures used in the model may not be accurate. The health utilities associated with the POAG stages were retrieved from the National Collaborating Centre for Acute Care (UK) [16]. According to the authors, however, the methodology adopted to estimate the values had not yet been validated. Besides, the original health utilities were estimated for different ocular conditions causing a defect in visual acuity, and might not be applicable to glaucoma patients since the pattern of visual loss in glaucoma differs from other conditions.

Probability of death could have also been underestimated under both interventions. In the absence of data to show that people die from glaucoma, I assumed that the probability of death among POAG patients was the same as that for the general population of Ghana. This assumption ignores the fact that the blind and people with visual impairment may have a higher probability of death from accidents.

I assumed that all patients who progressed from early POAG stage were given combination therapy. However, experts stated that some patients are shifted from one monotherapy to another before they are eventually given combination therapy, although the percentage of patients who fall into this category could not be estimated.

In addition, the assumption that the severity of the POAG condition is similar in both eyes of a patient may not reflect reality since, in practice, a patient could present with unilateral POAG.

Finally, the WTP threshold adopted in the study may not reflect the actual WTP threshold in Ghana. While the WTP threshold used in the model was based on DALYs averted, the study measured health effect in terms of QALYs gained. QALYs gained and DALYs averted may not be interchangeable since they are partly based on different assumptions and different methodologies.

#### 4.4. Conclusion

Given the existing evidence, prostaglandin analogue is not a cost-effective alternative to beta blockers as a first-line medication for primary open angle glaucoma in Ghana. Generic latanoprost may, however, be cost-effective in treating POAG patients 41 years and younger. The population EVPI shows that further research to reduce decision uncertainty would be cost-effective if expected cost of further research does not exceed USD 131 billion.

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**Appendix 1.** Mean Reduction in IOP from Baseline per Intervention.

Intervention	Mean Reduction
Beta Blockers	2.88 mmHg*
Prostaglandin Analogues	4.2 mmHg

\*mmHg (millimetres of mercury) is the unit of measure for intraocular pressure Source: (National Collaborating Centre for Acute Care (UK), 2009).

**Appendix 2.** Life Table for Ghana 2013.

Age	Probability of Death	
	Female	Male
<1 year	0.042299	0.0521
1 - 4 years	0.022923	0.024086
5 - 9 years	0.016682	0.016784
10 - 14 years	0.010198	0.009866
15 - 19 years	0.011471	0.013503
20 - 24 years	0.014199	0.01904
25 - 29 years	0.016908	0.020019
30 - 34 years	0.01927	0.021748
35 - 39 years	0.023739	0.026648
40 - 44 years	0.027454	0.030997
45 - 49 years	0.032665	0.039465
50 - 54 years	0.04376	0.054715
55 - 59 years	0.056971	0.069616
60 - 64 years	0.084521	0.101838
65 - 69 years	0.131772	0.151119
70 - 74 years	0.208545	0.228736
75 - 79 years	0.322648	0.345576
80 - 84 years	0.489874	0.520373
85 - 89 years	0.701343	0.715682
90 - 94 years	0.92976	0.947176
95 - 99 years	0.969188	0.975211
100+ years	1	1
100+ years	1	1

Source: <http://apps.who.int/gho/data/view.main.60630>.

**Appendix 3.** Unit costs of resources.

Resource	Unit of Pricing	Price (USD)	Source
Acetazolamide Tablet, 250 mg	Tablet	0.06	[38]
Pilocarpine Eye Drops	Bottle	3.38(a)	[38]
Timolol Maleate Eye Drops, 0.5%	Bottle	1.88	[38]
Latanoprost	Bottle	25.77(b)	Expert opinion
Trabeculectomy	1 Procedure	34.53	[39] [40]
Budesonide DPI, 200 micrograms	Inhaler(d)	18.82	[38]
Salbutamol Inhaler, 100 micrograms	Inhaler(d)	4.59	[38]
Fluticasone MDI	Inhaler(d)	18.72(c)	[38]
Beclometasone dipropionate Inhaler, 100 micrograms	Inhaler(d)	16.31	[38]

(a) Average cost for Pilocarpine Eye Drops 2% and Pilocarpine Eye Drops 4% (see appendix 2) (b) Average cost of generic latanoprost and branded latanoprost (Xalatan) (c) Average cost for Fluticasone MDI 125 microgram and Fluticasone MDI 250 microgram (see appendix 2) (d) All inhalers are for the treatment of asthma.



**Appendix 4.** One-way Sensitivity Analysis on Probability of Developing Asthma.

Annual Probability of asthma	Incr. Cost	Incr. QALY	ICER
0.00	1223426	104	11746
0.01	1223151	104	11715
0.02	1222873	105	11684
0.03	1222593	105	11653
0.04	1222310	105	11622
0.05	1222025	105	11591
0.06	1221737	106	11559

**Appendix 5.** One-way Sensitivity Analysis on Cost of Latanoprost (Excerpt).

Cost of Prostaglandin Analogues	Incr. Cost	Incr. QALY	ICER
13	506494	105	4821
14	562559	105	5355
15	618624	105	5888
16	674688	105	6422
17	730753	105	6956
18	786817	105	7489
19	842882	105	8023
20	898946	105	8557
21	955011	105	9090
22	1011075	105	9624
23	1067140	105	10158
24	1123204	105	10691
25	1179269	105	11225
26	1235333	105	11759

**Appendix 6.** One-way Sensitivity Analysis on Age of the Cohort (Ercerpt).

Age in Years	Incr. Cost	Incr. QALY	ICER
30	1295960	136	9495
31	1295090	136	9517
32	1294006	136	9541
33	1292658	135	9567
34	1290985	135	9594
35	1289583	134	9622
36	1288580	133	9654
37	1287326	133	9690
38	1285765	132	9730
39	1283826	131	9773
40	1281997	131	9819
41	1280350	130	9872
42	1278289	129	9931
43	1275720	128	9997
44	1272526	126	10068
45	1269536	125	10145
46	1266879	124	10233
47	1263554	122	10332
48	1259409	121	10442
49	1254252	119	10561
50	1249717	117	10690
51	1246130	115	10839
52	1241643	113	11010
53	1236054	110	11200
54	1229102	108	11408
55	1222439	105	11636
56	1216307	102	11899
57	1208639	99	12196
58	1199070	96	12527
59	1187133	92	12887
60	1176394	89	13277
61	1167576	85	13726
62	1156515	81	14231
63	1142638	77	14790
64	1125211	73	15396
65	1109913	69	16051
66	1098006	65	16797

**Appendix 7.** Two-way Sensitivity Analysis on Age of Cohort and Cost of Latanoprost (Excerpt).

Age in Years	Cost of Latanoprost (USD)					
	13	14	15	16	17	18
30	3922	4359	4795	5231	5668	6104
31	3931	4369	4806	5244	5681	6118
32	3942	4380	4819	5257	5696	6134
33	3952	4392	4832	5271	5711	6151
34	3964	4405	4846	5286	5727	6168
35	3976	4418	4860	5302	5744	6186
36	3989	4433	4876	5320	5764	6207
37	4004	4449	4895	5340	5785	6231
38	4021	4468	4915	5362	5809	6256
39	4039	4488	4937	5386	5835	6284
40	4058	4509	4960	5411	5863	6314
41	4080	4534	4987	5441	5894	6348
42	4105	4561	5018	5474	5930	6386
43	4133	4592	5051	5511	5970	6429
44	4163	4625	5088	5550	6012	6475
45	4195	4661	5126	5592	6058	6524
46	4232	4701	5171	5641	6111	6581
47	4273	4748	5222	5697	6171	6646
48	4319	4799	5278	5758	6237	6717
49	4369	4854	5339	5824	6309	6794
50	4423	4914	5405	5895	6386	6877