Cost-Utility of Tiotropium in Patients With Severe Asthma

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Research

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Abstract

Background

An important proportion of asthma patients remain uncontrolled despite the use of inhaled corticosteroids and long-acting beta-agonists. Some add-on therapies, as tiotropium bromide have been recommended for this subgroup of patients. The purpose of this study was to assess the cost-effectiveness of tiotropium as add-on therapies to ICS + LABA for patients with severe asthma.

Methods

A probabilistic Markov model was created to estimate the cost and quality-adjusted life-years (QALYs) of patients with severe asthma in Colombia. Total costs and QALYS of two interventions including standard therapy (ICS + LABA), add-on therapy with tiotropium, were calculated over a lifetime horizon. Multiple sensitivity analyses were conducted. Cost-effectiveness was evaluated at a willingness-to-pay value of $19,000.

Results

The model suggests a potential gain of 1.06 QALYs per patient per year on tiotropium, with a difference of US$ 478 in favor of tiotropium; showing dominance respect to standard therapy. A position of dominance negates the need to calculate an incremental cost-effectiveness ratio. In the deterministic sensitivity analyses, our base-case results were robust to variations of all assumptions and parameters

Conclusion

Add-on therapy with tiotropium was found to be cost-effective when added to usual care in patients who remain uncontrolled despite treatment with medium or high-dose ICS/LABA. Our study provides evidence that should be used by decision-makers to improve clinical practice guidelines and should be replicated to validate their results in other middle-income countries.

Summary At A Glance:

Add-on therapy with tiotropium was found to be cost-effective when added to usual care in patients who remain uncontrolled despite treatment with medium or high-dose ICS/LABA in a middle income country.

Background

Asthma is a disease that affects more than 300 million people worldwide(1). Trends suggest increasing asthma prevalence globally, with an anticipated 100 million new cases in the next decade principally in developing countries(2). For example, in Colombia, a nationwide Colombian study estimated a prevalence of 6.3% which is above that of many Latin American countries (3). Among chronic diseases, asthma is

one of the main contributors to increased health care expenditures. In the United States during the next 20 years is likely that the direct costs of asthma in adolescents and adults to be over $1.5 trillion (4).

At least 24% of the patients with asthma are classified as severe asthma requiring high doses of inhaled corticosteroids (ICS)-long-acting beta2-agonist (LABA) or ICS-LABA or oral corticosteroids (OCS) (5). Indeed despite these drugs, almost 70% of these patients do no achieve total control of symptoms (5). The direct cost of severe asthma per patient is three times higher than the cost of mild asthma; a cost that would be higher if we include indirect cost (6,7) .In this sense, severe asthma is a serious problem for health systems. In US Yaghoubi and colleagues calculates there will be 175 million person-years with uncontrolled asthma and if all those people with uncontrolled asthma in the United States can achieve and maintain asthma control, the saving would be about $300 billion in direct costs and $660 billion in indirect costs, recovering 15,462 quality-adjusted life-years(4).

In the last 20 years, new pharmacological alternatives have been developed for patients with severe asthma, among them the addition of long-acting muscarinic antagonists (LAMA), as tiotropium, to the current treatment with ICS-LABA (8). LAMA has demonstrated improves lung function and quality of life, and increased the time to severe exacerbation requiring OCS (9-11). Recent clinical guidelines recommend the use of add-on tiotropium to treatment with ICS-LABA in severe asthma (8). However, this recommendation raises concerns as if the extra benefit offered by this drug outweighs the additional cost compared to therapy with only ICS-LABA. This question is even more relevant in developing countries with an increasing prevalence of asthma and constrained healthcare. An economic evaluation of these new drugs could provide evidence to optimize the efficiency of the use of economic resources in these countries. This study aimed to use to assess the health and economic consequences of the three strategies of continuation of standard therapy, add-on therapy with tiotropium for the treatment of severe asthma in Colombia.

Materials And Methods

We conducted a probabilistic Markov model to estimate the cost and quality-adjusted life-years (QALYs) of patients > 18 years with severe asthma treated with tiotropium combined with medium-dose ICS/LAB in Colombia. The choice of time horizon was a lifetime. Two interventions were modeled: standard of care (ICS + LABA), add-on therapy with tiotropium. In this mathematical model, the patients could transition between four mutually exclusive health states (symptom-free state or asthma controlled on tiotropium and SOC and death). During each cycle, patients in non-death health states could transit to any of three levels of asthma exacerbations: OCS burst (was defined as asthma symptoms at least one week and need of use of oral corticosteroids , prescribed by a physician , to achieve the control of symptoms), emergency department (patients who experience an acute asthma attack and are treated in the emergency department with systemic corticosteroids) and hospitalization (Patient whom the physician decides to hospitalize due to failure of initial emergency room management) . Asthma-related mortality following an exacerbation or all-cause mortality could also occur (**Figure 1**). We made this analysis from a societal perspective (included direct and indirect costs), using a cycle length of 2 weeks.

Half-cycle correction and an annual discounting rate of 5% were applied to both costs and QALYs. Treatment was considered cost-effective if the incremental cost-utility ratio was below $ 19.000 per QALY gained using the World Health Organization (WHO) recommendation of three times the GDP per capita to define the willingness to pay (WTP) in Colombia.

Parameters of the Markov model

Multiple parameters were derived from published research and local data, which are presented in table 1. Data of relative risk (RR) on exacerbation rate were extracted from a recent cost-effectiveness study of tiotropium in patients with severe asthma (12). In this study, the relative risk was 0.72 (CI 95% 0.62-0.83), as from comparison of the incidence of exacerbation between patients with severe asthma treated with tiotropium combined with medium-high doses of ICS/LABA (n=274) versus management with only medium-high doses of ICS/LABA (n=822). Asthma exacerbations in this study were defined as the use of systemic corticosteroid burst, (or SCS, outpatient visits with at least three days of high-dose oral corticosteroids (OCS) or a single SCS injection) emergency department (ED) or hospitalization.

The transition probabilities for moving between different health states for the standard therapy and add-on therapy were derived from clinical trials and economic evaluations of tiotropium (13). Data of utilities of each Markov state were extracted from a systematic review of utilities in asthma (14, 15), **table 1**. This systematic review identifies a total of 20 studies in asthma that report utilities in different severity states of asthma. Within these four studies (n=330 patients) show a median utility of 0.74±0.029 for severe asthma, all estimated using time trade-off or standard gamble or Ashma symptom utility index in the US and UK population. Since all these data (RR, transition probabilities, and utilities) do not come from the Colombian population, they were subjected to probabilistic sensitivity analysis as detailed below, and as recommended by Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement(16). In this sensitivity analysis, to build the range of RR to be used in this analysis, we use the CI 95% of RR published by clinical trials and in real-life studies (9, 12). In the case of utilities and transition probabilities, the upper and lower range was estimated by adding or subtracting 25% of the value from the central value defined for the base case. The risk of mortality from other causes was estimated using age- and gender-specific Colombian life tables for all-cause mortality over 5 years (2016 to 2020) (17).

For tiotropium, we assumed that 28% of patients discontinued the treatment after 16 weeks of treatment (18). Patients who discontinued (non-adherents) treatment had the same costs and clinical outcome values as adherent patients for the first 16 weeks, but these input values change to those of the placebo group for all transition cycles after 16 weeks. Sensitivity analyses of percentage of non-adherents and response rate were made estimating the upper and lower range of each value by adding or subtracting 25% of the value defined previously

All costs of each health state defined in the Markov model were extracted from a previously published Colombian-based study (19). Briefly, this study identified the asthma-related direct and indirect cost of 1131 patients with severe asthma from January 1, 2004, through December 31, 2014, in Colombia.

Asthma severity classification was mainly based on the paper of Jacob et al (20,21). This group of patients with severe asthma had an average of 1.4 ED visits per year, and 2.5 hospitalizations per year; rates that are comparable to those reported in clinical trials and observational studies in patients with severe asthma and tiotropium use(9, 12). Unit costs of tiotropium were taken from the National Drug Price Information System (SISMED, 2020). All cost costs were transformed to 2020 costs using official inflation data in Colombia. We use US dollars (Currency rate: US$ 1.00 = COP$ 3,000) to express all costs in the study(17).

Sensitivity analyses

To explore parameter uncertainty of the model inputs, we conducted a probabilistic sensitivity analysis by randomly sampling from each of the parameter distributions (beta distribution in the case of relative risk and utilities, Dirichlet distribution for multinomial data in the case of transition probabilities, and gamma distribution in the case of costs). The expected costs and expected QALYs for each treatment strategy were calculated using that combination of parameter values in the model. This process was replicated one thousand times (i.e., second-order Monte Carlo simulation) for each treatment option resulting in the expected cost-utility. All analyses were made in Microsoft Excel®.

Results

The main results are presented in **Table 2**. For a patient with severe asthma, the base-case analysis showed that compared to SOC, treatment with the combination of SOC and tiotropium was associated with lower treatment cost and higher QALY. For SOC and tiotropium, the total discounted 10-years cost per person were US$ 12486 (CI 95% US$ 12436 to US$ 12535), and US$ 12008 (CI 95% US$ 11961 to US$ 12055) respectively. The QALYs per person estimated in the model for those treatments were 30.8 (CI 95% 30.7 to 30.9), and 31.8 (CI 95% 31.7 to 31.9) respectively.

In the analysis of the Markov cohort model, we estimated a median probability of surviving free of exacerbation of 0.547 in SOC and 0.51 of add-on therapy with tiotropium. The model suggests a potential gain of 1.06 QALYs per patient per year on tiotropium, with a difference of US$ 478 in favor of tiotropium; showing dominance respect to SOC. A position of dominance negates the need to calculate an incremental cost-effectiveness ratio.

Sensitivity analyses

In the deterministic sensitivity analyses, our base-case results were robust to variations of all assumptions and parameters. For none of the variables evaluated, variations within the established ranges led to the incremental cost-effectiveness ratio being higher than the WTP, **figure 2**. The results of probabilistic sensitivity analysis are graphically represented in the cost-effectiveness plane, **figure 3**. This scatter plot shows that compared with SOC, treatment with tiotropium tends to be associated with lower costs and higher QALY. Indeed, 67% of simulations were graphed in quadrant 2 (lower cost, high QALYs),

17% in quadrant 1 (high cost, high QALYs), 9% in quadrant 3 (lower cost, lower QALYs), and 6% in quadrant 4 (high cost, lower QALYs).

Discussion

This cost-effectiveness study estimates cost and QALY outcomes over a lifetime horizon for a hypothetical cohort of patients with uncontrolled asthma who had tiotropium added to their usual controller therapy .Our findings suggest that add-on therapy with tiotropium achieves better outcomes at a lower cost compared to standard treatment.

Our results are in line with previous studies. Hyng et al, using a similar Markov model as our study, tiotropium is a cost-effective alternative with an ICER $4,078/QALY in frequent SABA users and $8,332/QALY, on patient poorly controlled asthma (12). Despite our model have the same health states and uses the same relative risk, the healthcare systems in Colombia and Korea are different, leading to varying medical expenses. Indeed, our costs per event of OCR bust, ED visit, or hospitalization were 69%, 79%, and 46% less respectively than Korea. Another difference is the higher incidence rate of hospitalization due to exacerbation in the Hyng study concerning our study. The target population of Hyng study was elderly patients, but in our study was general adults and this can explain their higher rates. Willson et al using a six Markov model health states estimate an incremental cost-effectiveness ratio of £21,906 per QALY gained being tiotropium cost-effective in the UK(13). Despite our differences in the Markov model, relative risk, utilities, and cost; in this study, the target population was a general adult and their incidence rates were similar to our study. As is expected, the cost per event of OCS bust, ED visit, or hospitalization were higher five times in the UK than in our study in Colombia; and this can explain the differences in the magnitude of ICER between the studies. Zafari et al, using also a probabilistic Markov model with a 10-year time horizon and from a US societal perspective, found ICER of add-on therapy with tiotropium versus standard therapy, and omalizumab versus tiotropium was $34,478/QALY, and $593,643/QALY, respectively (22). Despite methodological differences between our and this study, such as the number of health states in the model, higher cost of drugs and another direct cost in the US, and utilities our conclusion is the same. One difference in our study to previous studies was the values of the utilities. The two previous studies use the utilities established in the Wilson study, which estimated them in the "PrimoTinAasthmatrial" population using the EuroQol EQ-5D tool in the UK population. We decided to use those reported in a systematic review to have broader values and in more diverse populations. Variations in the values of these utilities in the probabilistic sensitivity analysis did not significantly change the calculated ICER. Indeed , after of 10 000 simulations in our PSA tiotropium tends to be associated with lower costs and higher QALY; 84% of simulations were graphed in quadrant 1 o 2 of cost-effectiveness plane.

A not minor difference in our evaluation from previous studies is the fact that we have not only estimated the ranges of relative risks and transition probabilities using data from real-life studies but have adjusted our estimates for tiotropium adherence. Assuming 100% adherence is unrealistic and tends to overestimate the effect of tiotropium. On the other hand, including real-life study data increases the

external validity of the estimates themselves compared to just basing model inputs on data from controlled clinical trials.

A crucial methodological aspect is the discussion of willingness to pay (WTP) to declare in Colombia a cost-effective technology or not. Since Colombia does not have a threshold that represents the WTP per unit of effectiveness (QALY), the ICER results per QALY were evaluated by using the reference corresponding to the World Health Organization (WHO) recommendation (three times the GDP per capita). Not having an own estimate of the WTP may be debatable, however, up to now, all the economic evaluations in health carried out in the country follow the threshold suggested by the WHO, which has also been endorsed by the national technology evaluation agency (23). The results of the probabilistic sensitivity analyses confirm the robustness of the model results. Since transition probabilities and utilities do not come from the Colombian population, they were subjected to probabilistic sensitivity analysis as detailed below as recommended by Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement(16).

Our study has some limitations. We use utilities extracted from the literature and not estimated directly from our population. As was mentioned previously, the reliability and robustness of the results were evaluated by sensitivity analyses. Our result only refers to a patient with severe asthma uncontrolled by medium-dosage to high-dosage inhaled corticosteroids plus long-acting β-agonists, and cannot be extrapolated to patients with the use of oral daily corticosteroids. Studies of tiotropium in asthma have recruited both allergic and non-allergic asthma patients. By using evidence from such trials we assumed the same health benefits of tiotropium for allergic and non-allergic asthma patients and this assumption is supported by trials of tiotropium, which showed no difference between allergic versus non-allergic subjects (9).

In conclusion, add-on therapy with tiotropium was found to be cost-effective when added to usual care in patients who remain uncontrolled despite treatment with medium or high-dose ICS/LABA. Our study provides evidence that should be used by decision-makers to improve clinical practice guidelines.

Abbreviations:

inhaled corticosteroids (ICS)

long-acting beta2-agonist (LABA)

oral corticosteroids (OCS)

long-acting muscarinic antagonists (LAMA)

quality-adjusted life-years (QALYs)

standard therapy (SOC)

willingness to pay (WTP)

relative risk (RR)

Consolidated Health Economic Evaluation Reporting Standards (CHEERS)

Short-Acting Beta-Agonists (SABA)

Incremental cost-effectiveness rate (ICER)

Declarations

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of University of Antioquia (2015-4690)

Consent for publication: Not Applicable

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Tables

Table 1. Base case

Variable	Base case	Valor High	Valor Low	Reference
Cost Tiotropium (per 4 week)	$ 60	$ 75	$ 45	
Cost controlled (anual)	$ 2.244	$ 2.805	$ 1.683	(19)
Cost OCS burst (per episode)	$ 195	$ 244	$ 146	
Cost ED visit (per episode)	$ 228	$ 285	$ 171	
Cost hospitalization (per episode)	$ 4.635	$ 5.794	$ 3.477	
Utilities (anual)				
Utility of controlled state	0,740	0,93	0,56	(13)
Utility decrement				
Exacerbations requiring OCS burst	0,1	0,13	0,08	(14)
Exacerbations requiring ED visit	0,15	0,19	0,11	
Exacerbations requiring hospitalization	0,2	0,25	0,15	
Tiotropium efect				
Relative risk on exacerbation rate	0,72	0,83	0,62	(12)
Exacerbations				
Exacerbation anua rate	1,1	4	1	
# Hospitalization anual	2,6	5	1	
Adherence of Tiotropium	61%	76%	57%	(18)
Annual dicount rate	5,00%	6%	0%	

Table 2. Total cost

Health state	Cost (US$)	SE (US$)
1 month in controlled state	187	46,74
Cost/event OCS burst state	205	51,21
Cost/event : ED visit	208	51,97
Cost/event : Hospitalization	1.191	297,83
Cost Tiotropium (per 4 week)	45	23

Table 3. Cost- effectiveness of Tiotropium vs SOC

	Cost	Difference	QUALYs	Difference	C/E	ICER
Tiotropium	$ 12.008	$ -478	31,8	1,06	$377	
SOC	$ 12.486		30,8		$405	Dominated

Figures

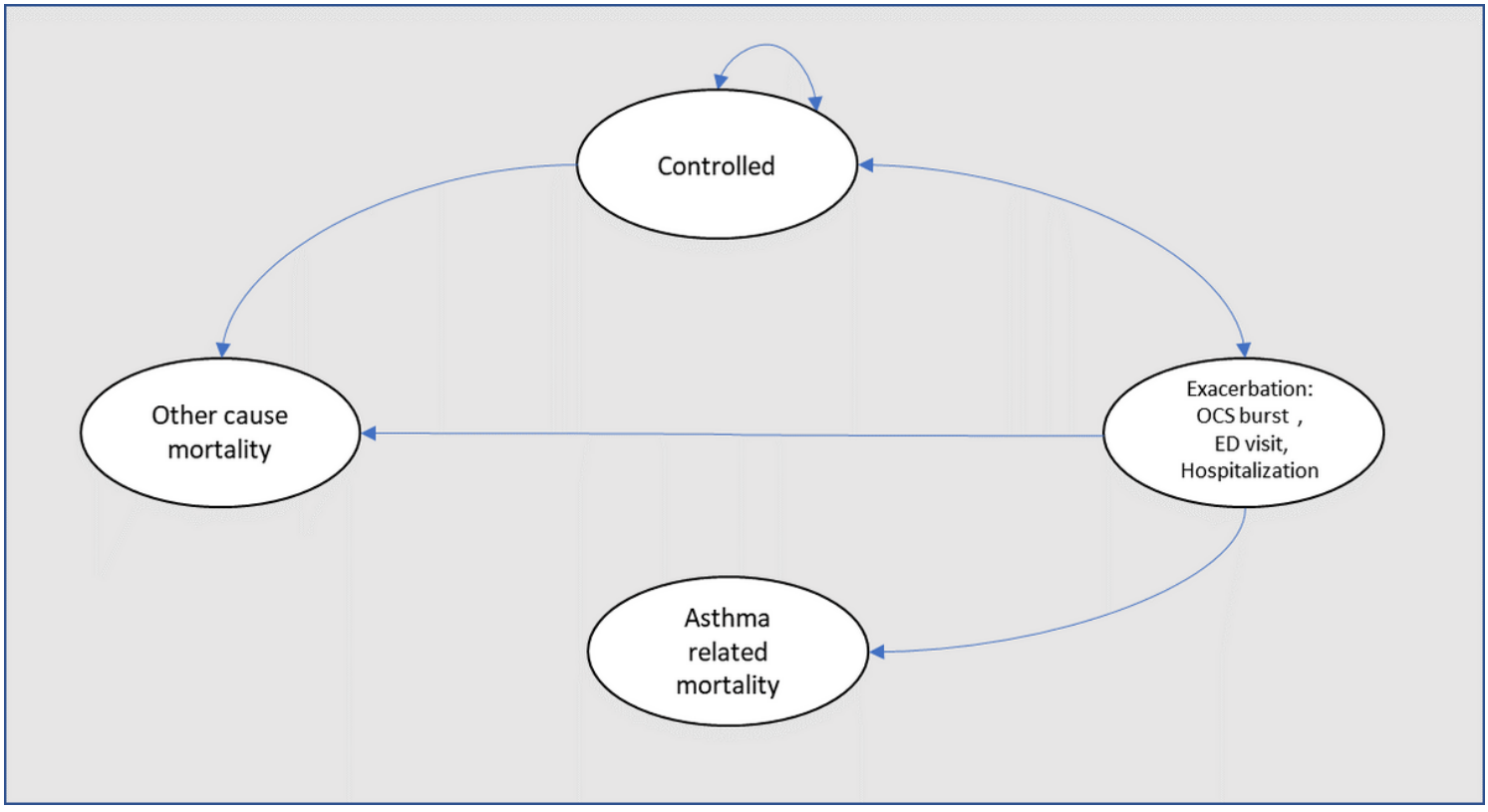

Figure 1

Markov model

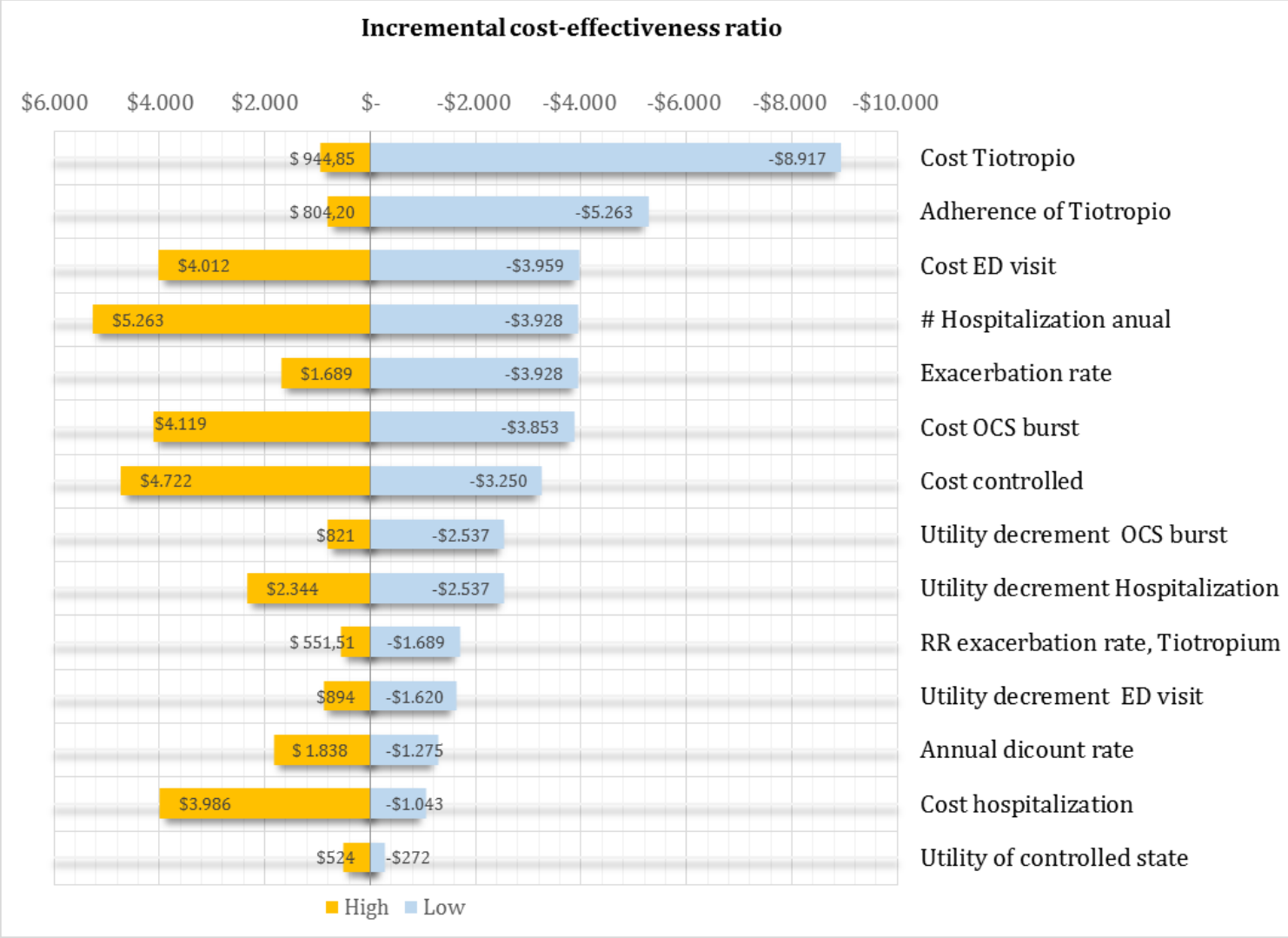

Figure 2

Tornado diagram.

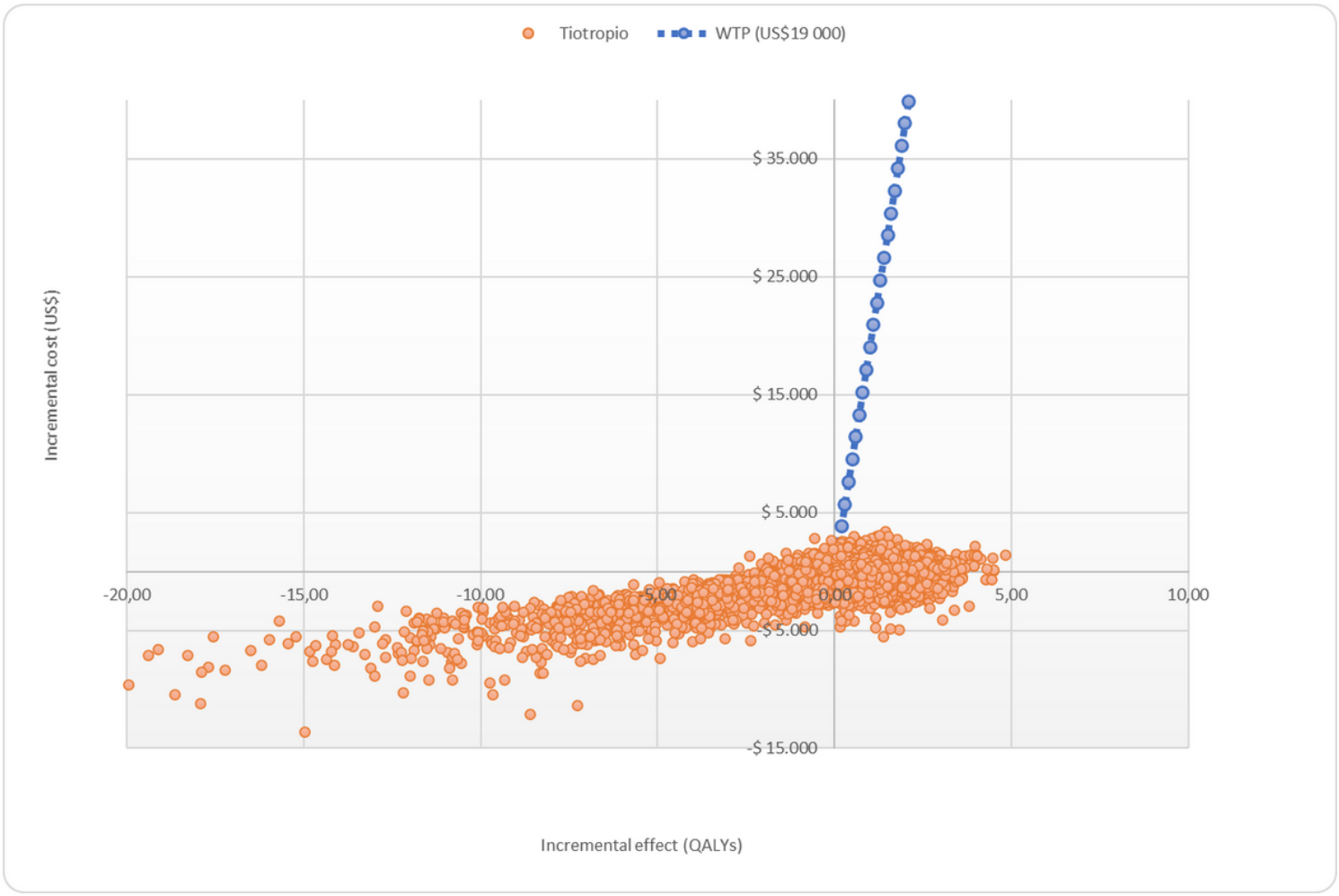

Figure 3

Cost effectiveness plane