Cost-Utility Analysis of Cryoballoon Ablation versus Radiofrequency Ablation in the Treatment of Paroxysmal Atrial Fibrillation; Case Study: Iran

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Research

Abstract

Background: Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia at which electrical stimulation does not pass a distinct pathway through heart. There are various methods to treat AF which Ablation is one of the most effective among them. The present study aimed to assess cost utility of Cryoballoon ablation (CBA) comparing to Radiofrequency ablation (RFA) to treat patients with AF in Iran.

Methods: Cost utility analysis is done using a decision analytic model based on a lifetime Markov structure which was drawn considering nature of interventions and natural progress of disease. Costs data was extracted from medical records of 47 patients of Rajaie Cardiovascular Medical and Research Center in Tehran in 2019. Parameters and variables related to strategies such as transition probabilities, risks related to side effects and mortality rates as well as utility values were extracted from domestic and foreign evidences. Due to uncertainty regarding some variables used in model, deterministic and probabilistic sensitivity analysis was also done. TreeAge pro 2020 were used in all stages of analysis.

Results: In the base case analysis, CBA strategy was associated with higher cost and effectiveness rather than RFA, and the incremental cost-effectiveness ratio (ICER) was $11223 per Quality adjusted life year (QALY), which compared to Iran one time GDP per capita ($7142) as Willingness to pay threshold, CBA was not cost effective. But on the other hand, considering twice the GDP per capita as threshold, CBA was cost-effective. Probabilistic sensitivity analysis confirmed findings of base case analysis, and Monte Carlo Simulation showed that RFA was cost effective by probability of 60%. One way sensitivity analysis showed that results of study has highest sensitivity to changes of RFA cost variable. The results of sensitivity analysis showed that the cost effectiveness results were not robust and are sensitive to changes in variables changes.

Conclusions: Primary results showed that CBA in treatment of AF comparing to RFA is not cost-effective in Iran considering one GDP per capita. But the sensitivity analysis results showed considerable sensitivity to changes of ablation costs variable. In general, it is not possible to conclude with certainty about the cost-effectiveness of CBA against RFA.

Introduction:

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia in which electrical stimulation does not pass a definite pathway, and occurs when electrical wave has not distinct direct in atria, and is described as supraventricular tachyarrhythmia which is accompanied by uncoordinated atrial activity and subsequently atrial mechanical failure (1).

Stages of AF are based on duration of arrhythmia which is classified into three paroxysmal, persistent and permanent stages. At paroxysmal stage, arrhythmia period is more than 30 seconds and shorter than one week, and if arrhythmia lasts for more than 7 days and lesser than one year, the disease will develop in persistent stage, and finally, if arrhythmia lasts for more than one year, the disease entered into permanent stage (2).

AF affected 21 million men and 13 million women based on 2010 data which prevalence rate is much more in developed countries (3, 4). According to present evidences, about one third of cardiac arrhythmia hospitalizations are due to AF which its rate has been increased up to 66% over last 20 years. This increase can be due to process of aging of the population, increase in prevalence of cardiac chronic diseases and increase of diagnosis cases due to advances in diagnostic technologies (5).

There are various methods to treat AF, which catheter ablation is one of the most important methods. Ablation is a non-surgical method that removes the region which consist abnormal pathway with specific waves. Nowadays this method is widely used to treat types of atrial tachycardia (rapid pulse rate), such as AF, atrial flutter, and some types of ventricular tachycardia. In this method, electrophysiologist inserts into heart cavities one or more catheters with electrodes at the end, and uses a type of energy to ablate the abnormal texture of heart, which causes extra electrical messages. The area of heart tissue which is ablated is too small and has no effect on total function of heart. In fact a small and safe repaired tissue in this area is formed and the normal rhythm of the heart will return (6, 7).

Ablation has various types. One type is point-by-point ablation around vessels using Radiofrequency ablation (RFA). In this method, a wire is entered through the groin, and the focal point of arrhythmia is burnt by entering these waves (7). Another type is Cryoballoon ablation (CBA). In this method, the physician enters a wire into heart through groin and places it at the focal point of arrhythmia. But this balloon is cooled through nitrogen flow, and focal point of arrhythmia is ablated through freezing. In uncoordinated arrhythmia of AF which has numerous focal points of the arrhythmia, one type of balloon could be used which spontaneously the focal points are frozen by nitrogen flow (7).

According to recent findings, ablation technologies are the most effective therapeutic methods to improve status of patients with AF and have the highest effect on preserving cardiac sinus rhythm as well as improvement quality of life (9, 10), but besides, also have different financial burden and risk load rather than other therapeutic methods.

There are various evidences regarding differences of two ablation technologies which some of these studies showed that these two methods have identical clinical efficacy and safety, and have almost low side effects and showed no considerable preference in none of methods (11, 12). But economically, studies around the world showed sometimes contradictory results regarding the cost-effectiveness of each method. In Iran, due to the fact that many years have not passed since the introduction and use of CBA, studies on comparing the costs and effectiveness related to this technology with other existing treatment methods are scarce.

In order to provide appropriate evidences to decide regarding application and coverage of the most appropriate technology, the current study was designed to assess cost-utility of CBA comparing to RFA to treat patients with AF in Iran.

Materials And Methods:

The present study is a full economic evaluation based on decision-analytic model which compared two strategies of CBA and RFA in Iran. Accordingly, the cost utility analysis method was used. Various stages of economic evaluation were performed based on reference guideline of national institute for health and care excellence (NICE) to perform economic evaluation of health projects (13).

Modeling

Designation of economic evaluation model was performed after literature review based on natural history of disease, process of performing ablation methods in patients with AF, clinical outcomes, probabilities of occurrence of outcomes and incidence of expenses.

In order to design the model, specialized panels were formed with the presence of a team of clinical specialists and economic team. After trial and error of various models, the final model was extracted by consensus and considering the most important clinical and economical outcomes based on natural history. The designed economic evaluation model is observed in Fig. 1.

The model structure is designed so that each strategy is based on a life time Markov structure with a one-year cycle length. In each Markov structure, five health states including AF before ablation, AF post intervention, AF post re-intervention, post stroke, normal sinus rythem (NSR) and death were considered. Individuals at both comparable groups were at the AF before ablation health state in zero cycle. Markov process of following cycles is so that individuals in each group and health states remained at the end of each cycle or went through other health states or died. Also patients can place at re-ablation state once, and due to lack of sufficient evidences, third ablations and higher were not considered in the model, and considering of AF post re-intervention health state was for this purpose.

In order to extract evidences regarding mortality rate and other evidences, mean age of 50 years (due to mean age of patients undergoing ablation based on accessible hospital information) for patients at initiation of Markov models were considered.

Extracting Parameters and Analyzes

This study was performed from the perspective of Iran health system and as mentioned, time horizon was considered as life time and costs and outcomes were estimated accordingly.

Since the current study was a full economic evaluation, QALY index was considered as outcome measure and its value at each health state is computed through estimating patients' utility at each state. Also, in this section, the amount of disutility caused by the side effects of ablation in health states was considered.

Status of cost effectiveness of each strategy was finally assessed based on cost per each units of QALY. Evidences related to patients' utility at each health state were extracted from international studies.

Regarding costs, due to study perspective, direct medical costs were only considered.

Costs of each strategy were estimated divided by costs of various of health states based on cost unit used in interventions. Costs of performing procedure of CBA and RFA including costs of CBA and RFA, costs related to management and supervision of receiving services in hospital, costs of hospitalization, supportive, therapeutic and pharmaceutical cares, and costs related to side effects were considered. Data collection for costing was from medical records of 47 patients of Shahid Rajaie Cardiovascular Medical and Research Center in Tehran in 2019. Since all the medical records related to 2019 were accessible, sampling was not done for this purpose, and hospital bills of all patients undergoing both ablation methods were assessed. Accordingly, 27 and 20 medical records related to CBA and RFA were assessed, respectively. Cost of other medical attempts required at health states independent from cost of procedure was determined based on therapeutic protocols. Accordingly, type of anti-coagulant and anti-arrhythmic medications and their doses until definite time, cost of hiring holter monitor device and cost of electrical cardioversion were determined. All the mentioned cases were different in various patients and therefore, by consultation with clinical consultant, a moderate amount of costs was considered. Cost of side effects was estimated based on evidences of previous studies and re-costing based on tariffs and domestic currency.

All the stages of costing was calculated by holding a specialized panel with clinical team and based on governmental tariffs of the Iran's Ministry of Health.

Other parameters and variables related to transition probabilities among health states of two strategies, risk of mortality at each health states, mortality risk caused by ablation methods, efficacy of interventions, and other parameters including risk of side effects of each ablation methods were extracted from international evidences. In this regard, based on each parameter, a distinct literature review was performed in scientific databases, and studies with appropriate evidences were classified and finally the best evidences were extracted.

Values of parameters and variables of the model and their references are given in Table 1.

Table 1
Model Inputs and Parameters

Statistic variable	Base case	SD/(CI)	Distribution	Source
Annual discount rate	0.05	(0-0.1)	Beta	
Time Horizon(year)	Life Time			
Probability of transition(CBA group)				
AF recurrence after ablation, first year	0.269	± 0.0538	Beta	(14)
AF recurrence after ablation, >first year	0.0938	± 0.0235	Beta	(15)
pericardial effusion or cardiac tamponade	0.0084			(14)
permanent phrenic nerve palsy	0.032			(14)
vascular complications	0.0156			(14)
Stroke rate per year	0.05			(16)
Re-intervention with RFA	0.5516	± 0.11032	Beta	(15)
Re-intervention with CBA	0..0951	± 0.01902	Beta	(15)
Probability of transition(RFA group)				
AF recurrence after ablation, first year	0.3326	± 0.0665		(14)
AF recurrence after ablation, >first year	0.1055	± 0.0264		(15)
pericardial effusion or cardiac tamponade	0.0231			(14)
permanent phrenic nerve palsy	0.0005			(14)
vascular complications	0.023			(14)
Stroke rate per year	0.05			(16,17)
Re-intervention with RFA	0.5685	± 0.1137		(15)
Re-intervention with CBA	0.0587	± 0.01174		(15)
Probability of death				
Annually probability of death (First year)	0.0057			Life Table
Probability of operative death	0.000487			(18)

Statistic variable	Base case	SD/(CI)	Distribution	Source
Stroke-specific mortality	0.3536			(19)
Costs($)				
AF average annual costs	372.81	± 55.92	Gamma	Survey and Calibration
NSR average annual costs	273.32	± 40.99	Gamma	Survey and Calibration
CBA	7751.88	± 516.72	Gamma	Survey and Calibration
RFA	5027.10	± 1530.66	Gamma	Survey and Calibration
Stroke costs, first year	1804.49	± 180.44	Gamma	Survey and Calibration
Post stroke costs, >first year	541.34	± 54.13	Gamma	Survey and Calibration
pericardial effusion or cardiac tamponade	1060.19	± 106.01	Gamma	(10), Calibration
permanent phrenic nerve palsy	11.09	± 106.01		(10), Calibration
vascular complications	60.23			(10), Calibration
Utilities				
NSR	0.8	± 0.00577	Beta	(20)
AF	0.6	± 0.0721	Beta	(20)
Post stroke	0.46	± 0.0577	Beta	(21)
Disutility due to complications	-0.0314		Beta	(22)
Disutility due to stroke, first year	-0.296		Beta	(23)

Cost effectiveness Analysis

In order to perform analysis and determine the most cost-effective strategy, due to costs and effectiveness of each strategy, incremental cost-effectiveness ratio (ICER) was calculated.

The equation for this index was as below:

$ICER = C_1 - C_2 / E_1 - E_2$

In which, $C_{1,2}$ represents for cost of CBA and RFA, and $E_{1,2}$ represents for their effectiveness.

Amount of ICER was compared with the amount of Iran's cost effectiveness threshold (WTP), and the most cost-effective strategy was determined.

In this study, cost effectiveness threshold was considered to be one times of GDP per capita equal to $7142 due to recommendation of WHO for developing countries.

In order to perform all stages of modeling and analysis of results, TreeAge 2011 software was used.

Sensitivity Analysis

Given uncertainty regarding some parameters used in the model, Deterministic and Probabilistic Sensitivity Analysis of the results of the model was performed.

In order to perform Deterministic Sensitivity Analysis (DSA), one way sensitivity analysis and Tornado diagram and two-way sensitivity analysis were used.

PSA was performed considering probability distribution of uncertain variables using Monte Carlo simulation. The range used for uncertainty in point estimation of each variable and statistical distributions used in PSA are presented in Table 1. In cases which no evidences regarding variance of the variable were found, 10–20% of mean values of variable was considered as standard deviation, and appropriate distribution was selected due to the type of variable.

Results:

Base Case Analysis

Table 2 represents results of cost utility analysis. Accordingly, the results showed that average life time costs per patient associated with CBA and RFA was $14198.3 and $12005.2, respectively. Average QALYs per patients were estimated 8.469 and 8.273 for both strategies, respectively. Accordingly, ICER was estimated at $11223.85 per QALY unit, which comparing to Iran's WTP threshold representing lack of cost-effectiveness of CBA technology compare to RFA.

Table 2
Results of Base Case Cost-effectiveness Analysis

Strategy	Cost($)	Incr Cost($)*	Eff**	Incr Eff***	ICER($/QALY)
RFA	12005.20	0	8.273	0	0
CBA	14198.36	2193.16	8.469	0.195	11223.85
*Incremental costs **Effectiveness ***Incremental Effectiveness					

Figure 2 also showed the cost-effectiveness plane of analysis. As observed, CBA strategy associated with higher costs and higher effectiveness than the RFA, and this amount of QALYs obtained in exchange for the increased cost due to CBA is not cost-effective based on considered threshold.

Sensitivity Analysis

Deterministic Sensitivity Analysis (DSA)

One-way DSA of all uncertain variables is presented in Fig. 3 using Tornado diagram. Variables includes cost of CBA, cost of RFA, probability of recurrence after CBA and RFA and probability of re-ablation using CBA in RFA group were considered for DSA. As observed in Fig. 3, changes in values of RFA cost had highest effect, and probability of recurrence after CBA had lowest effect on results of the study. Besides, based on diagram, all uncertain variables except for recurrence after RFA consist threshold and in distinct values change results of final analysis according to the considered confidence interval. It should be noted that in order to assess uncertainty of parameters more precisely, confidence interval of variables was considered widely.

Figure 4 shows results of one-way sensitivity analysis of RFA cost. As observed, this variable consists of threshold at value of $5738 (about $714 higher than base case), and at this value, results of cost utility analysis were changed and showed approximately high sensitivity analysis to changes of this variable. In order to assess more precisely, two-way sensitivity analysis was done based on changes of cost of CBA and RFA variables. As observed in Fig. 5, results of cost utility analysis show sensitivity to changes of these two variables.

In general, results of DSA showed that results of analysis have considerable sensitivity to changes of uncertain variables.

Probabilistic Sensitivity Analysis (PSA)

By considering function of probability distribution of uncertain variables, PSA was done using Monte Carlo simulation by considering number of 1000 times of repeating simulation and sampling. Figure 6 shows strategy selection diagram and optimization probability or in other words, cost-effectiveness probability of each strategy. Accordingly, as observed, cost-effectiveness probability of CBA and RFA was 41 and 59%, respectively, based on WTP threshold of $7142 per QALY.

Figure 7 shows that Incremental Cost Effectiveness scatter plot of CBA versus RFA in 1000 times of repeating sampling and simulation. In addition, Table 3 presented a report on probability of placement of CBA strategy at each cost effectiveness plot regions comparing to RFA strategy. As it is observed, probability of placement of CBA at regions of I, III, and IV and below WTP threshold (cost effectiveness regions) was 41%, and probability of cost-effectiveness of RFA was 59% which these results similar to above sections, confirmed base case analysis results.

Table 3
Report of the Cost-Effectiveness Probability in Each Cost Effectiveness Plane Quadrants

Component	Quadrant	Incre Eff(IE)*	Incre Cost(IC)**	Incre CE***	Frequency	Proportion (%)
C1	IV	IE > 0	IC < 0	Superior	142	0.142
C2	I	IE > 0	IC > 0	ICER < 3.0E8	263	0.263
C3	III	IE < 0	IC < 0	ICER > 3.0E8	2	0.002
C4	I	IE > 0	IC > 0	ICER > 3.0E8	332	0.332
C5	III	IE < 0	IC < 0	ICER < 3.0E8	4	0.004
C6	II	IE < 0	IC > 0	Inferior	257	0.257
Indiff	origin	IE = 0	IC = 0	0/0	0	0

*Incremental Effectiveness **Incremental Cost ***Incremental Cost Effectiveness

Discussion:

This study aimed to analyze comparative cost utility of two technologies of CBA and RFA in treatment of patients with paroxysmal AF in Iran.

Evidence review on these two novel technologies showed that in most countries they have better safety and efficacy rather than anti-arrhythmia medications in returning NSR (24–26). Regarding clinical efficacy of two technologies in treatment of AF patients, most review studies showed that there is no significant difference among two methods as well as their side effects, and in this regard, none of them is superior (7, 11, 27–28). Of course some other studies show a little superiority of CBA in this regard (14). Therefore, it seems that economic assessment of these two technologies through applying them in health care system is of most importance. Results of the present study showed that in base case analysis of CBA and RFA comparision, CBA is associated with higher costs and higher QALYs rather than RFA, and ICER was $11,223 per QALY, which based on the described WTP threshold ($7,142), CBA strategy was not cost-effective. Considering value of ICER equals to $11223, it can be said that CBA could be a cost-effective strategy at threshold of twice the of GDP per captia ($14,285).

Previous studies of comparing these two technologies in various countries also show controversial results.

For example, studies by Murray et al. (2018) in Germany and Sun et al. (2019) in china confirmed our findings (10, 29), in contrast, study by Ming et al. (2019) in China showed that CBA comparing to RFA is

dominant strategy in treatment of patients with AF due to lower cost and QALY values (15).

PSA of results also confirmed findings of base case analysis, and accordingly, results showed that by repeating sampling and simulation based on statistical distributions of uncertain variables, RFA strategy by probability of about 60% would be cost effective. DSA showed that results of analysis have higher sensitivity to changes of some variables, and in some values, variables have threshold and could change total results. Results of the study had highest sensitivity to changes of RFA costs. Accordingly, as observed, by increase in RFA costs from $5,127 to $5,738, the results will change and CBA will be cost-effective.

By more assessment on variables of RFA and CBA costs and considerable difference in cost of these two technologies, it was clarified that a part of this cost difference might be due to re-use of some necessities and not applying some sidelong tools in procedure of RFA which totally decreases costs of this intervention. This issue could increase risk of side effects and decrease efficacy of treatment considering comments of specialists, but since no appropriate evidences were found for this issue, it was not considered in economic evaluation model. In other words, decreasing in costs was considered in the model due to re-use of necessities, but negative outcomes related to that was not considered due to lack of appropriate evidences, which this issue increased chance of RFA for cost-effectiveness. Accordingly, it seems that results of study must be interpreted and used cautiously.

Present study is the first economic evaluation for comparison of ablation technologies in Iran. As mentioned, just hospital data of a specialized hospital was used, and due to lack of access to hospital data of other centers, comparison of costs at various centers was not achieved. Besides, since clinical studies regarding efficacy of technologies and associated side effects in Iran were not found, the best present evidences of international studies were just used. Another limitation of the study was regarding re-ablations. So that, appropriate evidences based on substitution of each technologies in case of failure of primary ablation were not found in Iran and thereby, international evidences were also used in this regard.

Conclusions:

Findings obtained from our study showed that based on viewpoint of Iran's Health system, CBA technology comparing to RFA is not a cost-effective strategy to treat patients with paroxysmal AF at threshold of one times of Iran GDP per capita. This is while, considering twice the GDP per capita and higher as threshold, CBA was cost-effective. On the other hand, results of sensitivity analysis showed that results of the evaluation model have considerable sensitivity to changes in uncertain variables such as ablation costs. In general, it is not possible to conclude with certainty about the cost-effectiveness of CBA against RFA.

Abbreviations

AF: Atrial fibrillation; RFA: Radiofrequency ablation; CBA: Cryoballoon ablation; NSR: Normal Synus Rythem; QALY: quality-adjusted life years; ICER: Incremental Cost Effectiveness Ratio; DSA: Deterministic Sensitivity Analysis; PSA: Probabilistic Sensitivity Analysis

Declarations

Ethics approval and consent to participate:

This research was approved by the ethical committee of Tehran University of Medical Sciences (TUMS) by the code of IR.TUMS.VCR.REC.1399.453.

Consent for publication

Not applicable

Availability of data and material

All data obtained during this study is included in this article. The datasets used and/or analysed during the present study are available from the corresponding author on reasonable request.

Competing interests:

There are no conflicts of interest that are directly relevant to the content of this article.

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Author contributions:

AD and ARD were in charge of collecting the data. RD and AD took the lead in writing the article. PS were in charge of clinical and specialized research sections. AD, RD did the modeling and analyses, interpreting the outcomes and edition the article. All authors read, edited and approved the final article.

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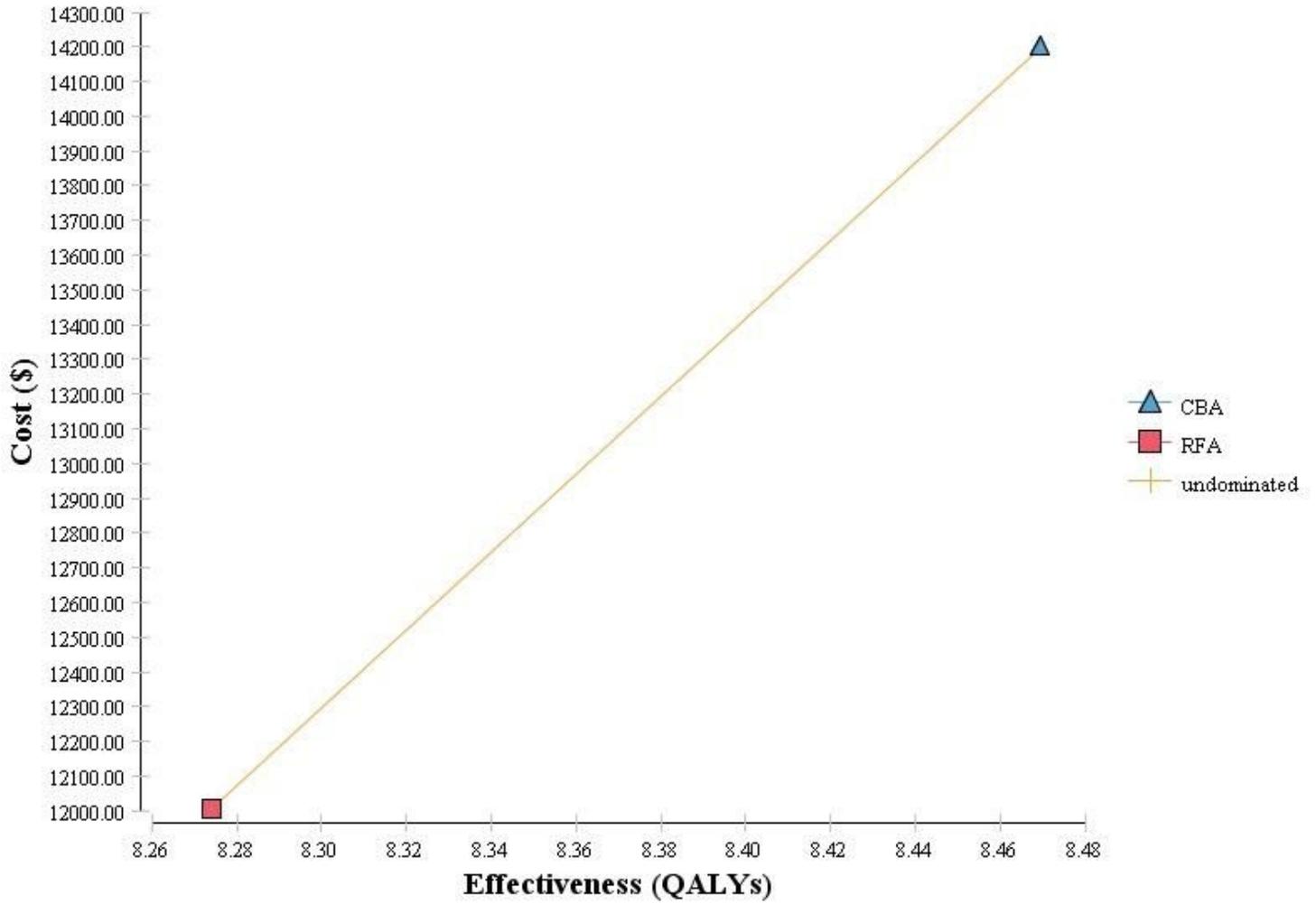
Figures

Figure 1

Markov Model for CUA of CBA vs RFA

Figure 2

Cost-Effectiveness Analysis of CBA vs RFA

Tornado Analysis (Net Benefits)

EV: 47094.531049371144

Legend:
- Cost_RFA
- P_AF_RF_AF
- Cost_CBA
- P_RF_Reinterv_CB
- P_AF_CB_AF

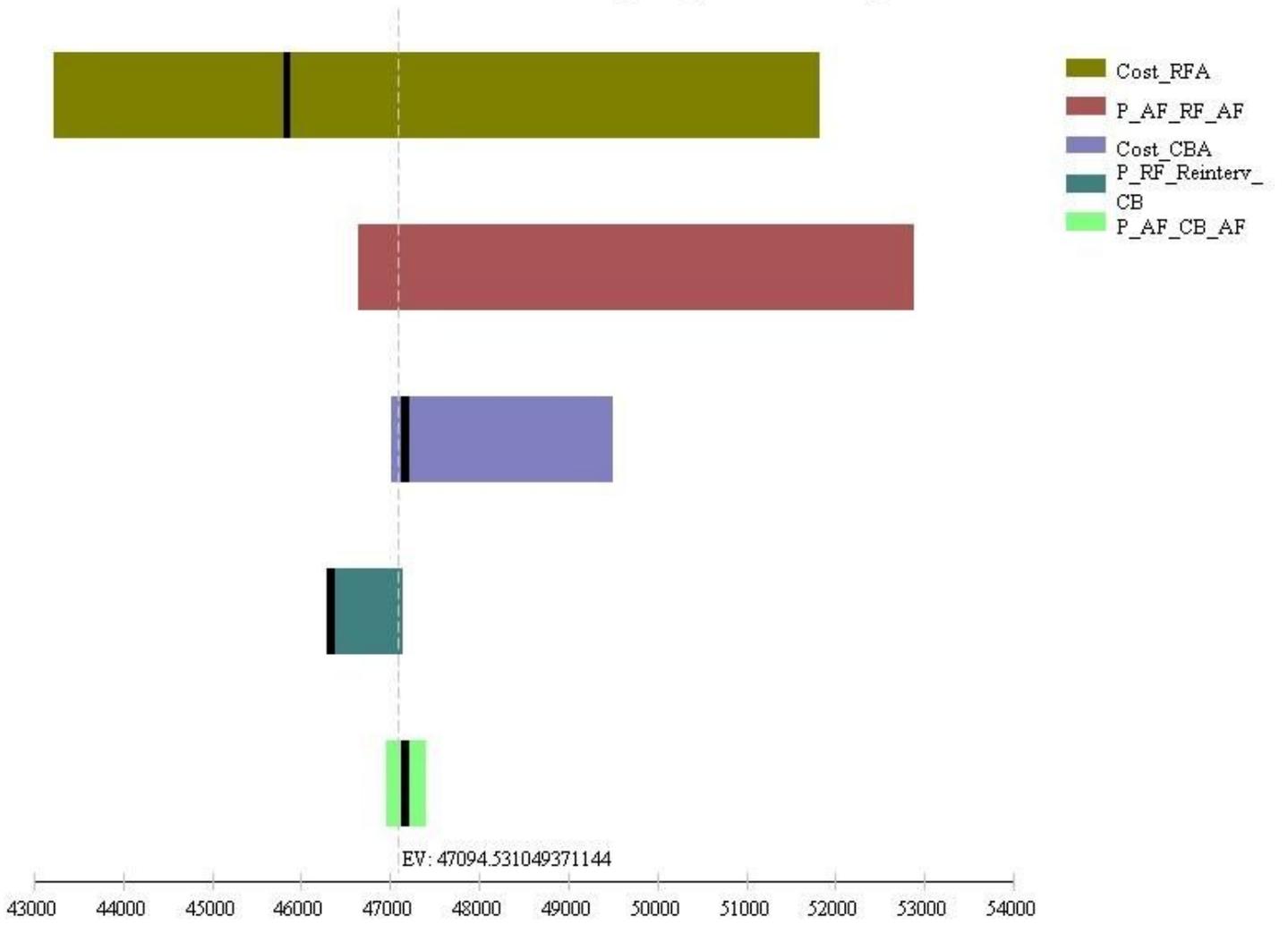**Figure 3**

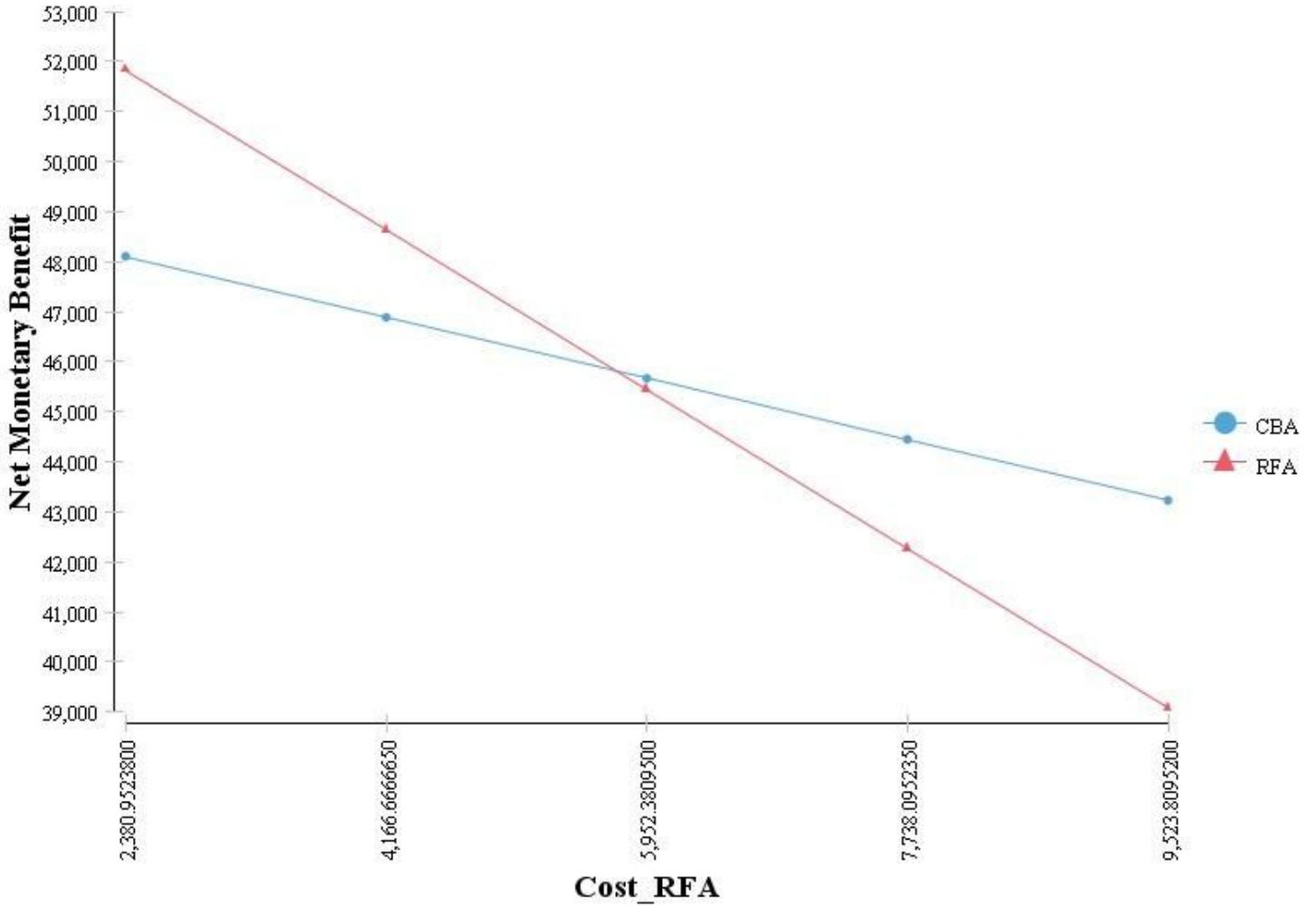One way Sensitivity Analysis using Tornado diagram

Figure 4

One way Sensitivity Analysis (RFA costs)

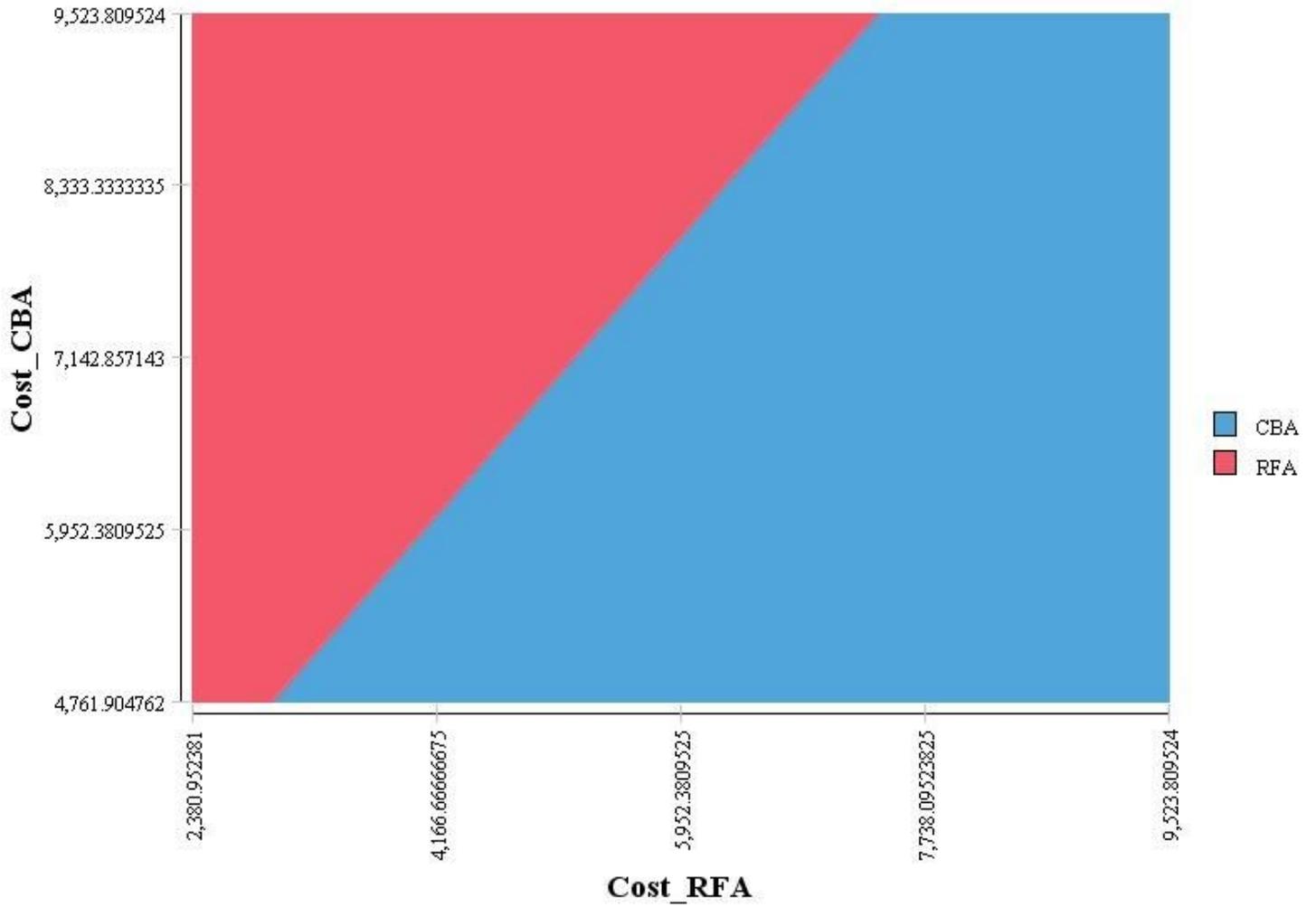**Sensitivity Analysis on Cost_RFA and Cost_CBA (Net Benefit, WTP=7142.857143)**

Figure 5

Two way Sensitivity Analysis (RFA Costs and CBA Costs)

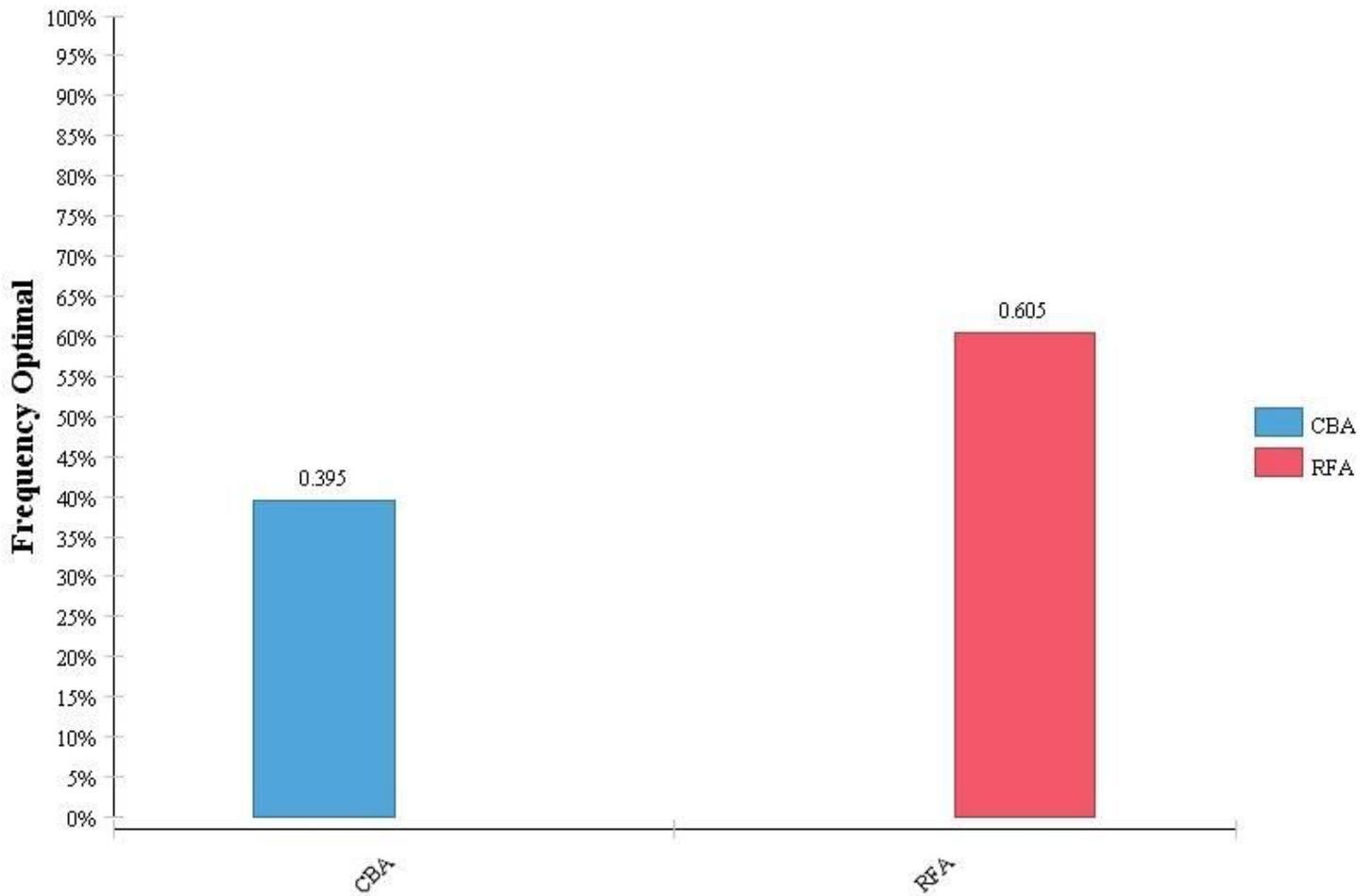**Monte Carlo Strategy Selection
(WTP: 7142.857143)**
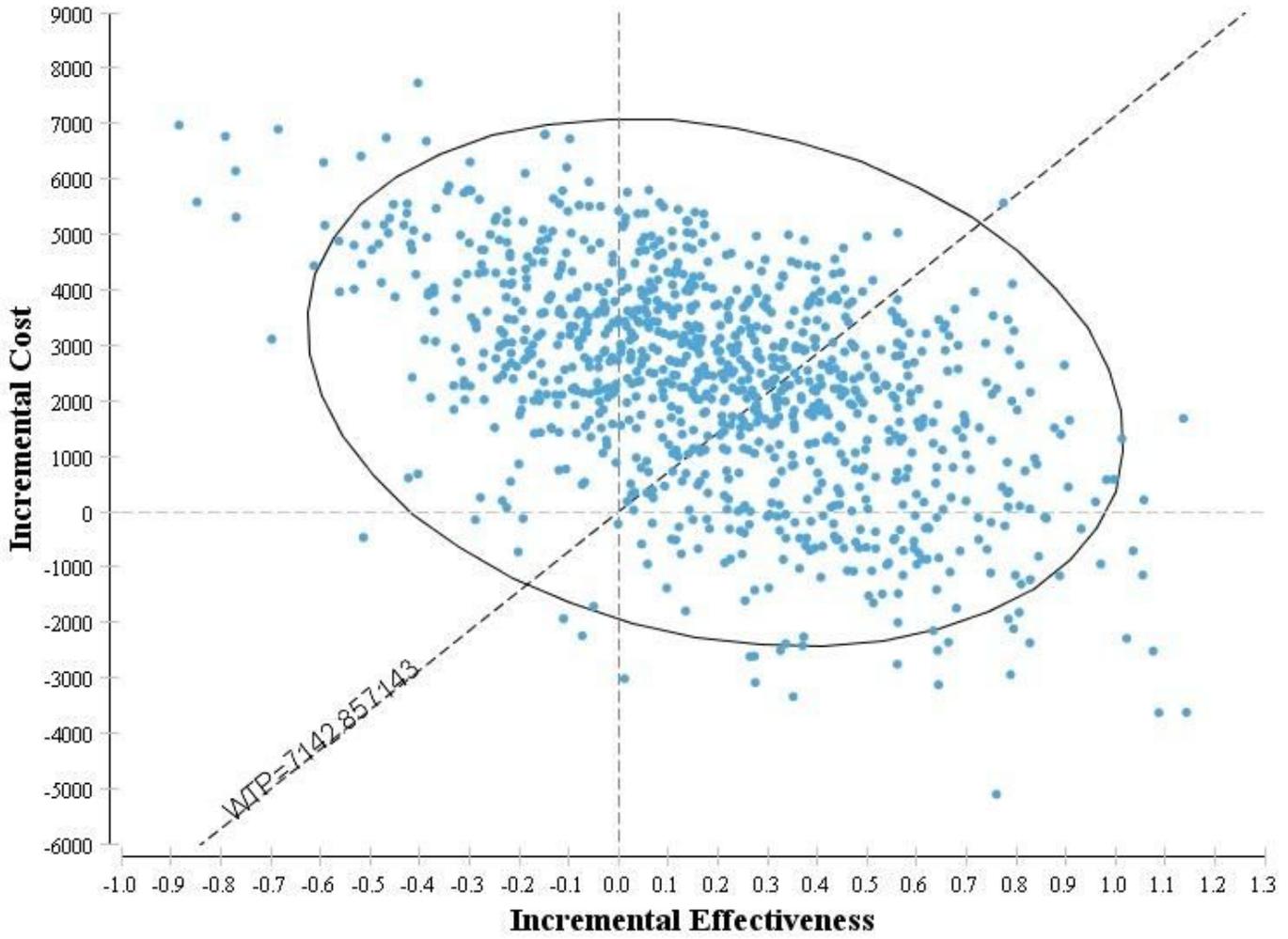
Figure 6

Strategy Selection Diagram and Optimization Probability

Figure 7

Incremental Cost-effectiveness Scatter Plot for PSA