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COST-UTILITY ANALYSIS OF PROSTATIC ARTERY EMBOLIZATION FOR TREATMENT OF LOWER URINARY TRACT SYMPTOMS

ABSTRACT

Purpose

To perform a post-hoc cost-utility analysis of a randomized controlled clinical trial comparing prostatic artery embolization (PAE) and transurethral resection of the prostate (TURP) in patients with lower urinary tract symptoms secondary to benign prostatic hyperplasia.

Materials and Methods

We conducted a cost-utility analysis over a 5-year period to compare PAE versus TURP from a Spanish National Health System perspective. Data were collected from a randomized clinical trial performed at a single institution. Effectiveness was measured as quality-adjusted life years (QALYs) and an incremental cost-effectiveness ratio (ICER) was derived from the cost and QALY values associated with these treatments. Further sensitivity analysis was performed to account for the impact of reintervention on the cost-effectiveness of both procedures.

Results

At the 1-year follow-up, PAE resulted in mean cost per patient of €2,904.68 and outcome of 0.975 QALYs per treatment. In comparison, TURP had cost €3,846.72 per patient and its outcome was 0.953 QALYs per treatment. At 5 years, the cost for PAE and TURP were €4,117.13 and €4,297.58, and the mean QALY outcome was 4.572 and 4.487, respectively. Analysis revealed an ICER of €2,121.15 saved per QALY gained when comparing PAE to TURP at long-term follow-up. Reintervention rate for PAE and TURP was 12% and 0% respectively.

Conclusions

Compared to TURP, in short-term PAE could be considered a cost-effective strategy within the Spanish healthcare system for patients with lower urinary tract symptoms secondary to benign prostatic hyperplasia. However, in long-term the superiority is less apparent due to higher reintervention rates.

Keywords: prostatic artery embolization (PAE); transurethral resection of the prostate (TURP); cost-effectiveness; benign prostatic hyperplasia

INTRODUCTION

Benign prostatic hyperplasia (BPH) is common among elderly males and its prevalence increases after the age of 40 [1]. Indeed, it has been estimated that 50% of men over 75 years of age have lower urinary tract symptoms (LUTS) because of BPH. Treatment options for BPH often include watchful waiting, medical treatment, and surgical or minimally invasive procedures. Transurethral resection of the prostate (TURP) is the gold standard treatment for medically refractory LUTS induced by BPH [2].

Prostatic artery embolization (PAE) has emerged as an alternative minimally invasive surgical therapy (MIST) for the management of LUTS due to BPH. In fact, PAE is an alternative to TURP that has comparable clinical outcomes in International Prostate Symptoms Score (IPSS) improvement, IPSS quality of life (IPSS-QoL) and International Index of Erectile Function (IIEF-5), with fewer complications and shorter recovery time. However, TURP significantly improves symptoms and urodynamic parameters such as maximum urinary flow rate (Qmax) [3–11]. The European Association of Urology (EAU) recommends offering PAE to people with moderate to severe LUTS considering minimally invasive treatment options and willing to accept less optimal objective outcomes compared to those achieved with TURP [2]. In addition, the National Institute for Health and Care Excellence (NICE) supports the use of PAE for LUTS secondary to BPH, provided that standard arrangements are in place for clinical management, consent, and auditing [11]. Nonetheless, guidelines from the American Urological Association continue to recommend further clinical investigation of PAE [12].

The evidence regarding economic factors when comparing PAE and TURP is still limited and to date, very few cost-effectiveness analyses comparing both procedures have been performed. A short-term (1 year) cost-utility analysis based on the UK-ROPE study [13] suggested that PAE is a cost-effective alternative to TURP in the first year, but that this benefit may be lost in subsequent years because of a higher reintervention rate. Furthermore, the Ontario Health Technology Assessment [14] concluded that cost-effectiveness analysis of PAE compared with TURP was uncertain over a time horizon of 6.5 years. In another study, Rink et al. [15] evaluated both procedures within the US healthcare system and reported that treatment via PAE was cost-effective over a time horizon of 5 years. In the same line, Wu et al. [16] recently concluded that PAE was a cost-effective strategy from the perspective of Medicare payers when considered over 3 years.

A randomized controlled clinical trial comparing PAE and TURP in patients with refractory LUTS showed similar results between both groups in terms of clinical outcome and IPSS-QoL, but its associated costs were significantly lower compared to TURP [3,17]. The most relevant cost differences were those arising during the interventional period, but no significant differences were observed during the 12-month follow-up. Here, is reporting a cost-utility analysis in which the variables of effectiveness and cost were considered over a time horizon of up to 5 years.

MATERIALS AND METHOTDS

This study followed the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [18]. We conducted a short (1 year) and long-term (5 year) post hoc cost-utility analysis to determine the costs and quality-adjusted life-years (QALYs) associated with PAE and TURP. This type of analysis was undertaken because utility inputs were available for our target population and a generic outcome measure such as QALYs allowed us to make comparisons across both interventions, scoring them from one for perfect health to zero for the value of death.

Data were derived from a randomized clinical trial performed in a tertiary Spanish National Health System (SNS) referral center for BPH (the University Hospital of Navarre) [3,17]. The trial was approved by the local ethics committee (code 49/2011) and was conducted from November 2014 to January 2017. Eighty-one patients with LUTS secondary to BPH were assessed for eligibility for the study. Details about the selection criteria and trial design can be found in the original study protocol [19]. Sixty one patients were randomized and, after patient exclusion due to not receiving the allocated treatment or discontinuing intervention, 54 patients were included in the one year analysis: 27 in the PAE group and 27 in the TURP group (bipolar resection). During the long-term follow-up, three patients were lost to follow-up (two in PAE at year three, and one in TURP group at year four). Therefore, 25 PAE and 26 TURP patients were considered in the 5-year period analysis. The patient flow diagram is represented in figure 1.

Costs of interventions

The costs for each participant were categorized according to the study period: pre-intervention (from obtaining informed consent until the operation), in-hospital (from the time of the intervention to hospital discharge), and follow-up (from the time of hospital discharge to the end of study). All the costs were covered by the SNS and were analyzed from a health care payer's perspective. After hospital discharge, the patients from both groups were followed up through scheduled visits at 1, 3, 6, and 12 months according to the clinical trial protocol, and afterwards for up to 5 years according to local standard clinical practice. The costs of the procedures involved in the study were provided by the Accounting Department at the University

Hospital of Navarre. PAE was performed under local anaesthetic compared with general anaesthetic for TURP. According to the type of intervention, the following costs were considered: the professional fees for the interventional radiologist or urological surgeons, costs of the operating facilities (nursing services, anaesthesiology staff, anaesthetic drugs, technical staff, equipment, imaging studies, histopathology, medical supplies required for the interventions, local anaesthesia for PAE and general anaesthesia for TURP, catheters, microcatheters, guidewires, and microspheres) and the stay in the recovery unit. The costs of the hospital stay also included the physician's professional fees, hospital pharmacy costs, and laboratory costs. PAE costs were calculated as outpatient setting. Administrative and accommodation (catering, laundry, and cleaning services) expenses were also included. During the trial, complications related to the urological process appeared in both groups and these costs were also considered. All mentioned costs were also considered when required reintervention. Over five years, the use of medication for BPH in each subject as well as its costs were analyzed. The willingness to pay (WTP) per QALY was set to €25,000, a realistic value for cost-effectiveness calculations in Spain [20], and a 3% annual discount rate was applied to both costs and effectiveness. The outcomes obtained were summarised using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Differences between PAE and TURP were compared using two-sided Student *t*-tests with a significance level of 0.05. Analyses were performed using Microsoft Excel 2016.

IPSS and Quality of life

BPH symptoms can significantly impact a person's quality of life (QoL). The IPSS comprises seven BPH-related LUTS which are categorized into obstructive and irritative symptoms. Patients in the study were asked at pre-intervention and 3, 6 and 12 months post-intervention to assign a score from 0 to 5 to indicate how often they experienced each symptom (0 being not at all and 5 being almost always). The breakdown score of the IPSS of each patient were converted into utility values using a correlation method suggested by Kok et al. [21]. The method of conversion of IPSS to utility values and the subsequent QALY values derived from each patient are available in appendix (tables A and B).

Main assumptions for long-term analysis

From twelve months after the intervention until five year, patients were followed-up according to local standard clinical practice, and during this period IPSS values of all patients were not routinely obtained. The he utility values for patients who had not undergone reintervention were assumed to remain stable until the study time limit of 5 years was reached (a 3% annual discount rate was applied). Participants who underwent a reintervention were assigned the mean utility value the group had prior to the first intervention. Patients who required urinary catheterisation were assigned the utility value of 0.831 referred in the study of Bermingham et al. [22].

Sensitivity analysis

A probabilistic sensitivity analysis was performed to address the uncertainty in the cost and effectiveness variables, developing the confidence ellipses at 50, 75, and 95% and cost-effectiveness acceptability curves. Additionally, a deterministic sensitivity analysis was conducted to further assess the influence of the input variables of early and late re-treatment rates. Three proposed scenarios with increasing early (up to year 2) and late (up to year 5) failure rates were studied. In scenario 1, an early reintervention rate of 20% PAE and 10% TURP and a late reintervention rate (annually) of 10% PAE and 1% TURP was proposed. In scenario 2, an early reintervention rate of 30% PAE and 10% TURP and late reintervention rate (annually) of 10% PAE and 1% TURP was considered. In scenario 3, an early reintervention rate of 40% PAE and 5% TURP and late reintervention rate (annually) of 10% PAE and 1% TURP was analyzed.

RESULTS

The cost breakdown of the two strategies (table 1) revealed that at one year follow-up, the mean costs per patient were lower for PAE (€2,904.68) than TURP (€3,846.72), meaning that this difference of €942.04 was statistically significant ($p = 0.009$). However, at the 5-year follow-up, the mean cost per patient between the procedures were comparable: €4,117.13 for PAE and 4,297.58 for TURP ($p = 0.762$). At the 1-year follow-up (table 2), the mean QALY outcome for PAE and TURP patients were 0.975 (95% CI [0.968; 0.981]) and 0.953 (95% CI [0.943: 0.962]), respectively. For the long-term analysis, the mean total QALY outcome for PAE was 4.572 (95% CI [4.525; 4.619]) and for TURP was 4.487 (95% CI [4.442; 4.532]). In short-term, the ICER revealed superiority of PAE but it becomes less favorable in the long-term follow-up.

During short-term follow-up, none of our study participants required a reintervention. However, over the long-term, three PAE patients (12%) required a step-up towards more invasive treatment. Two received TURP at year 3 post-PAE, which entailed additional costs of €3,514.62 and €3,249.11, and one at year 5 post-PAE underwent transvesical adenomectomy of the prostate at an extra cost of €7,148.95. The costs and QALY associated with these procedures were included in the PAE group. Additionally, a higher rate of patients in the PAE group (56% vs. 31%, $p = 0.772$) required medical treatment to manage prostatic symptoms during the long-term follow-up. This fact, added the reoperation in PAE patients, contributed to balance the long-term costs of both procedures. In the fifth year, two patients in the TURP group required urinary catheterisation because of BPH symptoms. During the follow-up, three patients died (for non-urological cause): two in PAE group (at year three) and one in TURP group (at year four). Exitus patients were not incurred in significant effect on the mean cost per patient and they were excluded from the long-term analysis. Finally, 25 PAE and 26 TURP patients were followed for the entire 5-year period.

Sensitivity analysis

The ICER point estimation and the 50%, 75%, and 95% confidence interval ellipses for the 12-month and 5-year follow-up are presented in figures 2 (a) and (b), respectively. The probabilistic sensitivity analysis showed that, at short-term, PAE was a less costly and more effective treatment strategy in all of the iterations. However, at long-term, both procedures tend to balance both in cost and effectiveness. The cost-effectiveness acceptability curve shows that at the 5-year follow-up, there was a 65% probability that cost-effectiveness was positive for any value of the WTP (figure 3).

Because the proposed ranges of early and late retreatment rates were varied, deterministic sensitivity analysis showed that a decrease in the costs and increase in QALY for TURP negatively impacted the cost-effectiveness of PAE. However, in the most restrictive setting (scenario 3) it also showed that increasing the early failure and late recurrence rate, the ICER for more effective PAE treatment resulted in additional costs of €15,346.81 per QALY, lower than the presumed WTP threshold (table 3).

DISCUSSION

This cost-utility analysis showed that, from a Spanish healthcare perspective, PAE was a more cost-effective strategy than TURP for the treatment LUTS caused by BPH. PAE was associated with a higher average QALY value and comparable costs over 5 years. This is the first cost-utility analysis using information derived from a clinical trial performed in a national healthcare center. Several economic studies previously showed PAE to be less costly than TURP in the short-term and from the healthcare provider perspective. Nonetheless, depending on the healthcare setting examined, significant differences in the cost of both procedures have been reported which ranged from 10% (Swiss setting) [23] to 65% (US setting) [24]. None of the previous studies contemplated the cost of follow-up except for our analysis, which covered the associated costs of both strategies up to 5 years post-intervention and resulted to be comparable.

Retreatment after TURP and PAE because of clinical failure or complications affect quality of life as well as costs. Multiple studies have already reported higher rates of early and late retreatments after TURP and PAE compared to our results. In this sense, Abt et al. reported that 21% of patients who underwent PAE required TURP within 2 years because of unsatisfactory clinical outcomes [4]. Furthermore, in the non-randomised UK-ROPE registry, the early retreatment rate was 19.9% for PAE and 5% for TURP after the same period of time [9]. To study PAE in the long-term, Bilhim et al. performed a retrospective study with more than 1,000 patients which described a reintervention rate of 21% at year 5 [25]. Moreover, an observational study from Germany reported that 87.1% of TURP patients did not need reintervention after 5 years [26]. In our study, patients were managed according to local standard clinical practice and only 3 individuals required reintervention. Therefore, there was an exceptionally low reoperation rate of 12% for PAE and 0% for TURP (although one patient in this group declined reintervention even though it was indicated). These findings may have been influenced by the small sample size we considered and by the selection criteria used for clinical trial.

To the best of our knowledge, very few cost-effectiveness studies comparing PAE with TURP have been published to date. In contrast to our real-case data, other work examined economic evaluations performed using simulation models with outcomes extracted from the literature. For instance, the Ontario Health Technology Assessment Series performed Markov modelling over a 6.5-year horizon in a Canadian context [14], showing that the cost-effectiveness of PAE versus TURP was 52% uncertain at a WTP of $50,000 per QALY gained. However, in contrast to the Spanish setting, the in-hospital costs of PAE and TURP were comparable. Two additional cost-effectiveness studies comparing both procedures using Markov modelling have been published from the US healthcare perspective [15,16]. Over time frame of 5 years, Rink et al. [15] concluded that as the ICER for the more effective TURP treatment resulted in almost five times higher than the assumed WTP threshold ($50,000 per QALY), therefore treatment via PAE could be assumed to be cost-effective. Recently, Wu et al. [16] used a comparative model over a 3-year time horizon to show that the ICER of TURP was more than 3 times the recommended WTP threshold of $100,000 and so PAE was considered to be a cost-effective strategy. This group obtained comparable effectiveness outcomes (2.845 QALYs from PAE versus 2.854 QALYs from TURP) albeit with a considerable patient cost difference (−$3,104) between both treatments. This contrasts with our study which found that there were differences in the effectiveness but not the long-term costs of PAE and TURP.

In the sensitivity analysis we performed, we proposed three scenarios in order to evaluate the effect of a higher rate of reintervention in our sample over the short and long-term, in the context of published cost-effectiveness studies. At five year, differences in the QALY outcomes for the PAE versus TURP strategy for scenarios 1 to 3 were decreasing 27%, 34% and 44%, and increasing differences in costs (22%, 173%, and 399%) respect our real-case data. For the three scenarios proposed, the ICER of the PAE strategy became progressively less favorable, although it remained below the accepted WTP threshold for Spain.

According to a recent review of patients' values, preferences, and expectations for the diagnosis and treatment of LUTS, men preferred less invasive management options with a low risk of adverse events, especially for sexual function [27]. One of the advantages of PAE is a shorter recovery time, eliminating the need for hospitalization, but assuming this strategy as an option if we are willing to accept less optimal objective outcomes. Existing literature on PAE suggest short-term IPSS improvement comparable with that of TURP but less effect on Qmax. In this study, a higher number of PAE patients required BPH medical therapy to manage prostatic symptoms after undergone the intervention, therefore we can assume that a higher proportion of these patients had experienced clinical failure.

We must bear in mind that this study had several limitations, including the fact that it was performed as a post hoc analysis, which has inherent limitations. The study evaluated costs specifically attributed to the national healthcare center and from a single-center perspective, which limits the generalizability of the results. Moreover, IPSS data were not systematically collected after 12 months. Therefore, we assumed that the treatments had stabilized the IPSS over a period of 5 years for any patients that had not been reoperated. However, because a limited number of long-term studies are available, some uncertainty remains about how long the effect of PAE treatment will last while surgical TURP treatments may have longer-lasting effects beyond 5 years. After one year, individuals were followed according local clinical practice, and may differ respect other settings. Although the costs related to the depreciation of equipment, electricity, security, medical records, and housekeeping were included, those of lost productivity, travel cost, or lost leisure time were not. Additionally, the limited number of subjects included in the analysis and the fact that they were selected for the clinical trial could have influenced the resulting utility outcomes and the low reoperation rates.

CONCLUSION

Several studies have demonstrated the clinical efficacy of PAE as an acceptable alternative for mild to moderate symptoms of LUTS due to BPH, with similar improvement in IPSS but less efficacy for urinary flow. In this study within the Spanish healthcare system, PAE could be considered cost-effective in short-term compared with TURP. However, the long-term superiority becomes less apparent based on the higher reintervention rates. The costs of both strategies were comparable and the minor utility differences are likely not clinically significant. The ICER estimated is associated with high uncertainty due to the small sample size and the methodology used. Further studies with large cohorts, in other healthcare settings, using real-world data, and comparing PAE versus ablative therapies or other MISTs, should be conducted to help choose the best therapeutic approach for each individual patient profile.

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Figure 1: Patient flow diagram

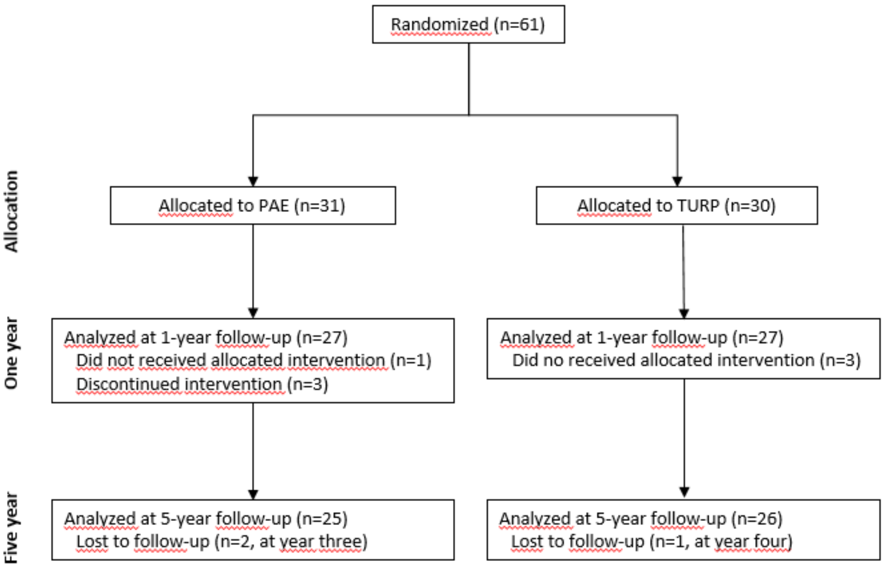


Table 1. Cost breakdown for the PAE and TURP patient groups

	PAE		TURP		
	Mean (€)	**SD**	**Mean (€)**	**SD**	***p*-value**
PRE-INTERVENTION	**307.37**	**130.17**	**263.62**	**71.32**	**0.163**
Clinical visit[a]	109.37	87.85	109.47	68.19	0.997
Pre-operative evaluation[b]	198.00	113.06	154.15	16.26	0.055
IN-HOSPTIAL	**1,771.60**	**346.89**	**2,849.13**	**826.30**	**< 0.001**
Interventional procedure	1,468.00	319.21	1,684.25	464.06	0.061
Recovery unit	0.00	0.00	163.23	107.24	< 0.001
Histopathology	0.00	0.00	152.22	27.82	< 0.001
Inpatient stay[c]	303.60	48.45	849.43	439.31	< 0.001
1-YEAR FOLLOW-UP	**825.71**	**1,570.50**	**733.97**	**543.44**	**0.782**
Clinic visit[a]	287.74	93.01	276.34	110.78	0.712
Complications	360.00	1,482.36	194.58	398.65	0.586
Other[d]	177.97	94.18	263.05	98.32	0.003
COSTS AT ONE YEAR	**2,904.68**	**1,562.79**	**3,846.72**	**926.54**	**0.009**
FROM YEAR-2 TO YEAR-5	**1,158.24**	**1,726.32**	**419.08**	**623.11**	**0.053**
Clinic visit[e]	248.27	268.59	198.26	202.70	0.510
Reoperation[f]	468.82	1,432.44	0.00	0.00	0.115
Prostatic medication	441.14	627.63	220.82	509.57	0.176
COSTS AT FIVE YEAR*	**4,117.13**	**2,768.66**	**4,297.58**	**1,049.65**	**0.762**

[a]Urology and/or intervention radiologist clinic and primary care clinic; [b]imaging (transabdominal ultrasonography, CT angiography for PAE, or X-ray for TURP), laboratory tests, pre-anaesthesia visit for TURP; [c]hospitalisation (PAE as outpatient setting), laboratory tests, and hospital pharmacy; [d]laboratory tests and pharmacy; [e]urology clinic; [f]two TURP and one transvesical adenomectomy of the prostate. *PAE n = 25, TURP n =26. Three reinteventions in PAE and none in TURP group.

Table 2: Economic analysis results

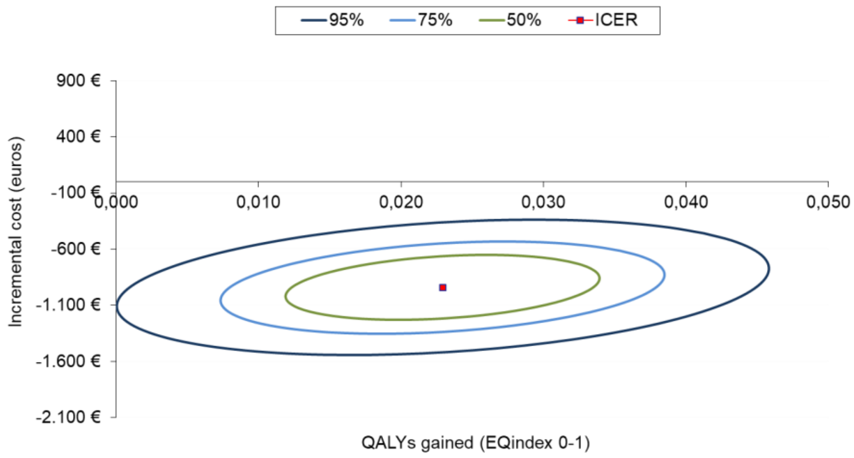
Alternative	Mean cost (€) (95% CI)	Incremental cost (€) (95% CI)	Mean QALYs (95% CI)	Incremental QALY (95% CI)	*p* -value	ICER (€/QALY)
At one year follow-up*						
PAE	2,904.68 (2,315.20; 3,494.16)	−942.04 (−1,598.45; −285.62)	0.975 (0.968; 0.981)	0.022 (0.010; 0.034)	0.002	−42,792.74
TURP	3,846.72 (3,497.23; 4,196.20)		0.953 (0.943; 0.962)			
At five years follow-up†‡						
PAE	4,117.13 (3,031.83; 5,202.42)	−180.45 (−1,337.87; 976.96)	4.572 (4.525; 4.619)	0.085 (0.016; 0.154)	0.021	−2,121.15
TURP	4,297.58 (3,894.12; 4,701.04)		4.487 (4.442; 4.532)			

*PAE $n = 27$. TURP $n = 27$
†PAE $n = 25$. TURP $n = 26$
‡Added values during the five years
QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio

Figure 2: Confidence ellipses for PAE versus TURP for the incremental cost (vertical axis) per incremental outcome gained (horizontal axis) at (a) the 1-year follow-up and (b) the 5-year follow-up. The contour lines of the confidence ellipse on the cost-effectiveness plane represent those combinations of effectiveness and incremental cost for which the density function remains constant, in these cases at the 50%, 75% and 95% level of confidence.

QALYs: quality-adjusted life years

a)



b)

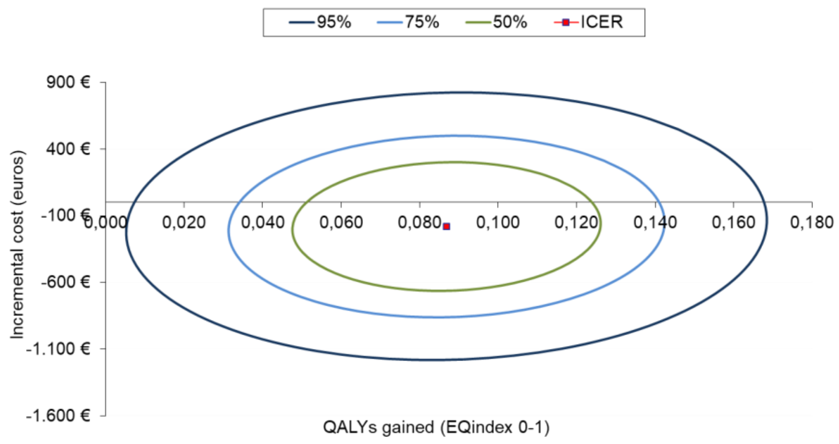


Figure 3: Five year follow-up cost-effectiveness acceptability curve for PAE versus TURP for the probability of cost-effectiveness (vertical axis) versus a range of cost-effectiveness willingness to pay values per incremental outcome gained (horizontal axis).

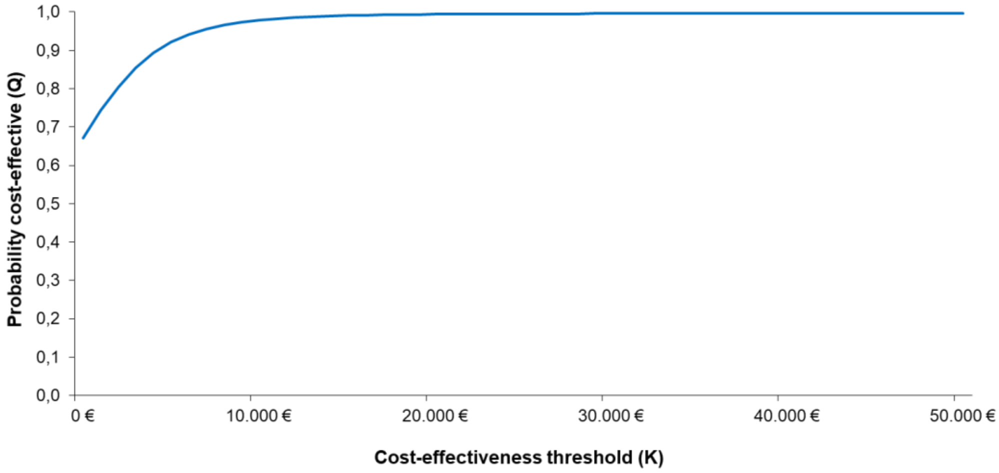


Table 3: Scenarios for the deterministic sensitivity analysis at year 5*

	Mean cost (€) (95% CI)	Incremental cost (€) (95% CI)	Mean QALYs (95% CI)	Incremental QALY (95% CI)	*p* -value	ICER (€/QALY)
Scenario 1: Early reintervention rate: 20% PAE and 10% TURP. Late reintervention rate (annually): 10% PAE and 1% TURP						
PAE	4,660.39 (3,937.10; 5,383.69)	38.84 (−766.06; 843.74)	4.548 (4.507; 4.589)	0.062 (-0.03; 0.127)	0.047	625.04
TURP	4,621.55 (4,218.09; 5,025.02)		4.486 (4.442; 4.529)			
Scenario 2: Early reintervention rate: 30% PAE and 10% TURP. Late reintervention rate (annually): 10% PAE and 1% TURP						
PAE	4,932.98 (4,209.69; 5,656.27)	311.43 (−493.48; 1,116.33)	4.542 (4.501; 4.583)	0.056 (-0.009; 0.121)	0.072	5,555.36
TURP	4,621.55 (4,218.09; 5,025.02)		4.486 (4.442; 4.529)			
Scenario 3: Early reintervention rate: 40% PAE and 5% TURP. Late reintervention rate (annually): 10% PAE and 1% TURP						
PAE	5,205.57 (4,482.7; 5,928.86)	720.30 (−84.60; 1,525.21)	4.536 (4.495; 4.577)	0.047 (-0.018; 0.112)	0.131	15,346.81
TURP	4.485,26 (4,081.80; 4,888.73)		4.489 (4.446; 4.532)			

*Added values during the five years
QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio