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ORIGINAL RESEARCH

Cost-effectiveness of percutaneous patent foramen ovale closure as secondary stroke prevention

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ABSTRACT

Objective: Compared to medical therapy alone, percutaneous closure of patent foramen ovale (PFO) further reduces risk of recurrent ischemic strokes in carefully selected young to middle-aged patients with a recent cryptogenic ischemic stroke. The objective of this study was to evaluate the cost-effectiveness of this therapy in the context of the United Kingdom (UK) healthcare system.

Methods: A Markov cohort model consisting of four health states (Stable after index stroke, Post-Minor Recurrent Stroke, Post-Moderate Recurrent Stroke, and Death) was developed to simulate the economic outcomes of device-based PFO closure compared to medical therapy. Recurrent stroke event rates were extracted from a randomized clinical trial (RESPECT) with a median of 5.9-year follow-up. Health utilities and costs were obtained from published sources. One-way and probabilistic sensitivity analyses (PSA) were performed to assess robustness. The model was discounted at 3.5% and reported in 2016 Pounds Sterling.

Results: Compared with medical therapy alone and using a willingness-to-pay (WTP) threshold of £20,000, PFO closure reached cost-effectiveness at 4.2 years. Cost-effectiveness ratios (ICERs) at 4, 10, and 20 years were £20,951, £6,887, and £2,158, respectively. PFO closure was cost-effective for 89% of PSA iterations at year 10. Sensitivity analyses showed that the model was robust.

Conclusions: Considering the UK healthcare system perspective, percutaneous PFO closure in cryptogenic ischemic stroke patients is a cost-effective stroke prevention strategy compared to medical therapy alone. Its cost-effectiveness was driven by substantial reduction in recurrent strokes and patients' improved health-related quality-of-life.

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Introduction

Most cases of cryptogenic ischemic stroke are embolic in origin, involving thrombi that travel to the cerebral vasculature after arising in proximal arteries, in the heart, or, in the presence of a right-to-left shunt, in the veins[1]. Patent foramen ovale (PFO) is significantly associated with cryptogenic stroke, and paradoxical embolism via a PFO is an important cause of unexplained infarcts in young and middle-aged adults[2]. Among young and middle-aged stroke patients, ~30% of ischemic strokes are considered cryptogenic, when no major cause for the stroke is identified after diagnostic investigation[3,4]. Young cryptogenic stroke patients have fewer risk factors for atherosclerosis (such as hypertension, diabetes, and smoking), and they are less likely to have peripheral vascular disease. Given the relatively young age of cryptogenic stroke patients and their cardiovascular risk factors, there is no reason to believe that their life expectancy would be shorter than the age-adjusted general population once appropriate secondary stroke prevention treatments are implemented.

Common chronic symptoms after stroke include weakness (e.g. hemiparesis), loss of sensation, speech and language disorders (dysarthria, dysphasia), cognitive impairments, and visual defects (e.g. hemianopia). Additional late effects of stroke include dementia, depression, post-stroke epilepsy, spasticity, and fatigue. Post-stroke fatigue is common and often severe, and can continue for years, affecting many aspects of everyday life[5,6]. Depression is also common and affects one-third of stroke survivors. Quality-of-life adjusted survival during the 10 years following an index stroke or transient ischemic attack (TIA) is low, with initial stroke severity and recurrent stroke being major predictors[7].

Stroke has high societal economic costs, totaling ~£9 billion a year in the UK[8]. Nearly half of stroke costs are direct

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Supplemental data for this article can be accessed here.

care costs, one-quarter are due to informal care costs, and income lost to productivity and disability accounts for the remainder. The average acute and rehabilitation care cost per stroke patient in the UK is currently £23,315[9]. Given the young age of many patients with PFO-related cryptogenic ischemic stroke, ongoing annual costs can extend over a considerable period of time.

It follows that an intervention which reduces the risk of recurrent stroke may lead to improved health-related quality-of-life and increased potential for an independent, fulfilling life. Among young to middle-aged patients who experience cryptogenic stroke due to presumed paradoxical embolism, percutaneous PFO closure has been recently shown to be superior to medical therapy alone in preventing recurrent ischemic strokes[10–14].

The aim of this study is to evaluate the cost-effectiveness of device-based PFO closure using the AMPLATZER PFO Occluder (Abbott), in addition to medical therapy compared to medical therapy alone for secondary stroke prevention. The target population is young and middle-aged patients with a PFO and a first cryptogenic ischemic stroke. The study uses the UK healthcare system perspective with an aim to contribute to NHS England's evaluation of PFO closure technology.

Methods

Model overview

A Markov model was developed to compare the clinical and economic outcomes of percutaneous PFO closure plus medication to medical therapy alone. Rates of recurrent ischemic stroke were extracted from a sub-population of the RESPECT trial[13] with the anatomical features of the PFO that would likely to be considered for percutaneous closure in the UK[15], such as an atrial septal aneurysm and/or substantial right-to-left interatrial shunt. We refer to this patient cohort as the UK sub-population. One-time costs of PFO closure procedure, device, adverse events, and follow-up care were developed from NHS sources. Cost of recurrent stroke treatment and quality-of-life were derived from the literature. All costs were converted to 2016 Pounds Sterling.

The model had a 20-year time horizon, with 3-month cycles. Outcomes were evaluated annually, up to 20 years. A half-cycle correction was made at the beginning and at the end of the Markov process[16]. Projected outcomes and costs were discounted at 3.5%, following the recommendations of National Institute for Health and Care Excellence (NICE). The analysis used the UK NHS perspective. The software used was TreeAge Pro 2016 (TreeAge Software, Inc., Williamstown, MA).

Patients

Modeled patients represent a sub-population of patients enrolled in the RESPECT trial (ClinicalTrials.gov number, NCT00465270), a multi-center, randomized, open-label, controlled clinical trial with blinded adjudication of end-point events[13]. The trial was approved by each site's institutional review board, and all patients provided written informed consent. Trial patients were randomly assigned, in a 1:1 ratio, to receive medical therapy alone or to undergo closure of the PFO with the Amplatzer PFO Occluder. The RESPECT trial enrolled patients who had a history of cryptogenic ischemic stroke, were 18–60 years of age, and had a PFO that was confirmed by transesophageal echocardiography. There was no restriction of the PFO anatomy, but patients were excluded from RESPECT trial participation if a mechanism for the qualifying stroke other than presumed paradoxical embolization could be identified. Complete enrollment criteria are provided in the RESPECT publication Supplementary Appendix Table S3[13]. Comprehensive cardiac and neurological evaluations to determine the etiology of the qualifying stroke performed during the RESPECT trial were similar to the NHS standard-of-care protocols implemented in the NHS hospitals[17]. The PFO closure group in RESPECT trial received aspirin plus clopidogrel daily for 1 month, followed by aspirin monotherapy for 5 months. Further anti-thrombotic therapy after 6 months post-PFO closure was at the discretion of the patient's physicians, and over 85% received ongoing anti-platelet therapy.

To make the cost-effectiveness analysis more generalizable to the real-world UK patient population, the modeled cohort was similar to a patient sub-group identified by a recent survey of UK specialists[18]. That survey suggested that patients with cryptogenic stroke with atrial septal aneurysm and/or large shunt size and no additional traditional risk factors would be considered for PFO closure in the UK. Therefore, the modeled patient cohort was RESPECT trial patients with a cryptogenic ischemic stroke and putative high risk anatomical features of the PFO atrial septal aneurysm and/or substantial right-to-left inter-atrial shunt who required no anti-coagulation for their concomitant conditions, and could be managed on anti-platelet medication (the UK sub-population). Moreover, in this analysis, we aligned the stroke prevention medication regimen with the NHS guidelines. The medical therapy group received anti-platelet therapy (75 mg dose of clopidogrel daily), and the PFO closure group received aspirin plus clopidogrel daily for 1 month, followed by aspirin monotherapy. The starting age for modeled patients was 46, to match the mean age of patients in the RESPECT trial, which was 45.9 years old.

Model structure

Four health states modeled the natural history of patients: Stable post-index stroke, Post-Minor Recurrent Stroke, Post-Moderate Recurrent Stroke, and Death (Figure 1). A hypothetical patient cohort transitioned from one health state to another, following transitional probabilities (Table 1).

For both treatment arms, patients started the Markov process in the Stable state. Patients remained in the Stable state until they experienced either a recurrent stroke event (minor or moderate) or death. Patients who experienced a minor recurrent stroke were moved to Post-Minor Recurrent stroke, and stayed in that state until either a moderate recurrent stroke or death occurred. Patients who experienced a moderate recurrent stroke from the Stable or Post-Minor Recurrent

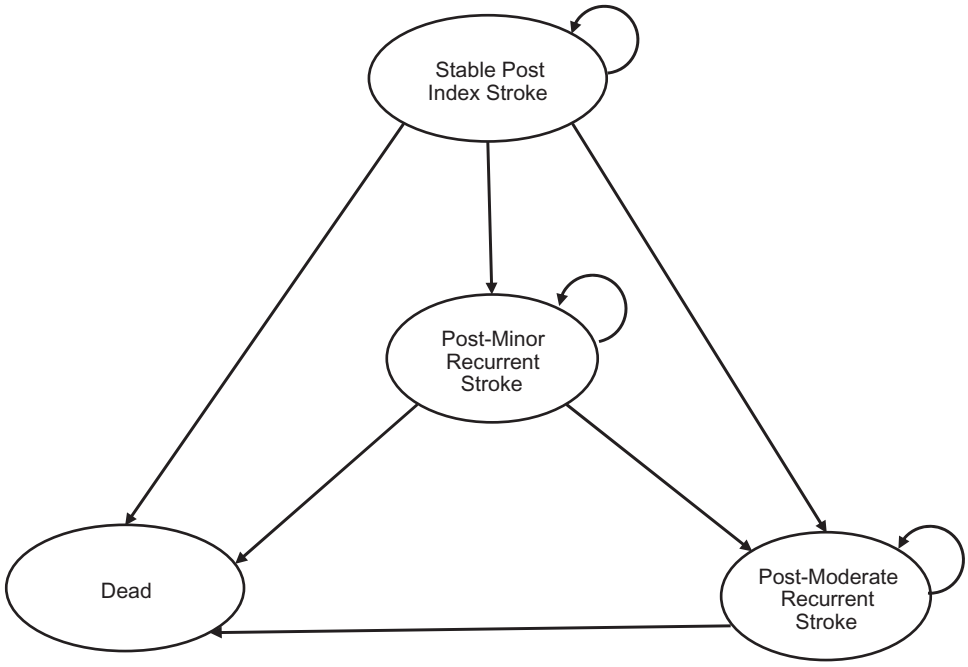

Figure 1. Markov process for cost-effectiveness of percutaneous PFO closure.

Stroke states moved to Post-Moderate Recurrent stroke, and remained there until death. Patients in Post-Moderate Recurrent Stroke could transition only to the Death state. Costs and benefits were accrued through modeled time horizon or until death.

Transition probabilities

Ischemic stroke event rates were extracted from the original data of the RESPECT trial[13,15] for the UK sub-population. All annualized probabilities were converted to quarterly probabilities to correspond to the cycle length. The probabilities of recurrent stroke and mortality are presented in Table 1. In the base case, 30% of the recurrent ischemic strokes were assumed to be moderate severity and 70% were minor severity, based on expert opinion, and confirmed by co-authors caring for cryptogenic stroke patients. The assumption was supported by RESPECT trial data, in which ~40% of recurrent stroke patients had a modified Rankin Scale global disability score of 2 or greater[3,19].

To model the safety profile and estimate serious adverse events (SAEs) associated with the AMPLAZER PFO Occluder, we used the original data of the RESPECT trial. The long-term RESPECT trial results suggested that PFO closure had an acceptable safety profile, and the overall rate of SAEs between the two groups were not different[13]. For this analysis, however, the model conservatively included procedure- and/or device-related SAEs that required additional healthcare utilization in the cost of PFO closure procedure. Given that most of the observed SAEs occurred about the same time as the procedure and were acute in nature, the SAEs data were included in the initial cycle immediately post-PFO closure procedure.

Throughout the modeled cycles, at any stage, patients could die from other causes or from the increased risk of death due to recurrent stroke. Background mortality rates were based on the UK 2015 Life Table, which provided age- and gender-specific mortality rates[20]. In this analysis, average values of the gender-specific mortality indices were used. Hence, patients in the Stable state were subject to mortality, simply due to the natural process of aging. Increased risk of death due to recurrent stroke was based on a UK population study on long-term outcomes of cryptogenic strokes[21]. Our annual post-stroke mortality rate was developed from the 10 years mortality follow-up after cryptogenic stroke reported in Li *et al.*[21]. In this model, the increased risk of death due to stroke was the same for minor and moderate strokes.

Cost and resource use

This analysis assumes that the AMPLATZER PFO Occluder was used as the PFO closure device. Cost categories were one-time PFO closure treatment, follow-up medical therapy treatment, and acute and follow-up stroke care (Table 1). The total PFO closure treatment cost was £6,644, which included procedure and device cost (£6,300), routine follow-up (£271), and treatment cost of SAEs which would be incurred by the NHS (£73). Because there is no NHS tariff for the PFO closure procedure, the procedure and device cost of the AMPLATZER PFO Occluder was assumed to be £6,300, which was based on the NHS England price in the Commissioning through Evaluation project of PFO closure to prevent recurrent stroke, inflated to 2016 Pounds Sterling (£) using the consumer price index[22,23].

Routine follow-up testing was transthoracic echocardiographic assessment with a bubble study (National tariff of £271). Procedure- and/or device-related SAEs that required new or prolonged medical treatment or repeat PFO closure procedures (£73 per each patient implanted) were estimated

Table 1. Base case parameter assumptions for cost-effectiveness of percutaneous PFO closure.

Parameters	Base value	Reference
Transition probabilities		
Recurrent Stroke, annual		
PFO Closure	0.36%	RESPECT Trial[15]
Medical Therapy	1.310%	RESPECT Trial[15]
Moderate severity of stroke	30%	RESPECT Trial[19] and expert opinion
Minor severity of stroke	70%	RESPECT Trial[19] and expert opinion
Post-stroke death, annual	4.5%	Li *et al.*[21]
Other causes death	2015 UK Life Table	Office for National Statistics[20]
Costs		
One-time PFO closure treatment, per patient		
Procedure and device	£6,300	NHS England
Device- or procedure-related SAEs	£73	National Tariff
Routine follow-up care	£271	National Tariff
Total cost	£6,644	
Stroke, first 12-month costs		
Minor stroke	£10,281	Luengo-Fernandez *et al.*[24]
Moderate stroke	£16,111	Luengo-Fernandez *et al.*[24]
Post-stroke, annual costs after 1 year		
Minor stroke	£2,328	Luengo-Fernandez *et al.*[24]
Moderate stroke	£3,648	Luengo-Fernandez *et al.*[24]
Anti-thrombotic medication, annual		
Aspirin, 75 mg	£5	NHS[27]
Clopidogrel, 75 mg	£40	NHS[28]
Utilities		
Stable state		
Medical therapy alone	0.80	Lin *et al.*[37]
Within 6 months post-PFO closure	0.84	Lin *et al.*[37]
6 months post-PFO closure and thereafter	0.88	Lin *et al.*[37]
Post-minor stroke		
First 6 months	0.73	Luengo-Fernandez *et al.*[7]
Thereafter	0.75	Luengo-Fernandez *et al.*[7]
Post-moderate stroke		
First 6 months	0.50	Luengo-Fernandez *et al.*[7]
Thereafter	0.62	Luengo-Fernandez *et al.*[7]
Dead	0.00	

from careful review of the RESPECT trial SAE source documents and application of the NHS clinical protocols for SAE management[13]. Of the 25 device- and/or procedure-related SAEs in the RESPECT trial, five SAEs would have required an additional NHS payment, due to post-discharge care: atrial flutter or fibrillation (1), residual shunt requiring additional PFO closure (2), pulmonary embolism (1), and an episode of sepsis and endocarditis (1). The remaining 20 SAEs were transient or peri-procedural, and would have been treated during the hospitalization for PFO closure procedure. The costs for these SAEs incurred by the hospitals due to additional procedures or extended hospital stay were added to the one-time PFO treatment cost. In the RESPECT trial patients treated with PFO closure were less frequently treated with anti-coagulation than the medical-therapy group, which may have contributed to the reported higher rate of venous thromboembolism, e.g. pulmonary embolism in the PFO closure group. Among the patients in the PFO closure group in the RESPECT trial, the propensity to venous thromboembolic events was particularly strong in the sub-group of patients who had previous, clinically manifest, unprovoked deep-vein thrombosis. This analysis assumes that patients requiring anti-coagulation for any reason will not be considered for PFO closure. Therefore, pulmonary embolism not related to device or procedure was not included in this model, since the risk of this event is assumed to be the same across the arms.

The cost of recurrent strokes came from a recent UK population-based cohort study by Luengo-Fernandez *et al.*[24], which reported 5-year mean hospital care costs after minor, moderate, and severe strokes (Oxford Vascular Study). A majority of the 5-year costs were incurred soon after stroke. Cost of care during the first year after stroke was reported to be ~53% of the 5-year cost, due to the initial hospital admission and intense rehabilitation; after the index admission, costs were driven more by lower cost outpatient services[24,25]. During subsequent years, reported hospital costs fluctuated slightly around 9–14%, with an average of 12% of the 5-year total which was used for this analysis. This model separated hospital costs incurred in the first 12 months from the subsequent annual hospital costs incurred for the rest of patients' lives (Table 1).

All costs in currency other than Pounds Sterling and in years other than 2016 were converted to 2016 Pounds Sterling. Conversion to Pounds Sterling was based on data reported by the Organization for Economic Co-operation and Development (OECD) for the UK. The purchasing power parity (PPP) was used to convert 2009 US dollars to 2009 Pounds Sterling[23]. Year 2009 Pounds Sterling values were converted to 2016 values using the consumer price index (CPI) for medical services[23].

Cost of medications was based on the NHS perspective, and was estimated based on the pricing of British National Formulary 2016[26–28].

Health-related quality-of-life (QoL)

Utility values assigned for each health state were based on a UK population-based study (Oxford Vascular Study) reported by Luengo-Fernandez *et al.*[7]. The authors assessed the long-term health-related quality-of-life (QoL) in patients after stroke and reported the EQ-5D health state utility values for minor, moderate, and severe strokes over 5 years.

In the Luengo-Fernandez *et al.*[7] UK population-based study, stroke-free patients that were matched on co-morbidities with stroke patients had a utility of 0.86 at 5 years. Patients in our study had prior stroke, but were younger than those in the Luengo-Fernandez *et al.* study. Expert opinion of the authors suggested an initial health state utility of 0.80 for both the PFO closure and medical-therapy groups (Table 1). For post-implant, one study suggested that patient QoL increased as much as 20% compared to pre-implant[29], but the improvement reflected not only resolution of psychological distress, but also in part recovery from the index stroke during the study time period and an enrichment of the population for patients with post-stroke migraines. Further support of increased utility following PFO closure was recently published. Mirzada *et al.*[30] compared QoL for PFO closure patients with non-closure patients and an age- and gender-matched reference group. While the PFO closure group had similar QoL compared to the reference group, the non-closure group had lower scores compared to the PFO closure group on physical functioning, role limitation-physical, vitality, and general health—suggesting that PFO closure improved QoL[30]. Therefore, this analysis took a conservative approach, and assumed that PFO closure therapy would improve utility by 10% starting from 3 months post-procedure. To account for potential discomfort for the first 6 months, post-procedure utility was assumed to have a modest improvement of 5%. Therefore, patients in the PFO closure group had a utility of 0.84 for the first 6 months post-procedure and 0.88 thereafter.

Throughout the course of the modeled lifetime, patients may suffer subsequent recurrent strokes. In their UK population-based study, Luengo-Fernandez *et al.*[7] reported health state utility up to 5 years after minor and moderate strokes. Health impairment from minor stroke reduced utility to 0.73, followed by small increases. Health impairment from a moderate stroke reduced utility to 0.50, with increases at 6- and 12-months post-stroke. We used an average of those short-term and long-term utilities in the model. If the recurrent stroke was minor, the utility score was reduced to 0.73. If the recurrent stroke was moderate, the utility score was reduced to 0.50. Those utility scores lasted for 6 months after stroke, then increased to 0.75 following minor recurrent stroke and 0.62 following moderate recurrent stroke (Table 1). Death was assigned a utility of zero.

Model outcomes

The model was developed to simulate short- and long-term costs and quality-adjusted life years (QALYs). The primary outcome was estimates of incremental cost-effectiveness ratios (ICERs) at various time points. The ICER was calculated by dividing incremental costs by incremental QALY gains. The commonly accepted willingness-to-pay (WTP) threshold of £20,000 recommended by NICE in the UK was used to ascertain the cost-effectiveness of PFO closure[31].

Table 2. Sensitivity analyses ranges for cost-effectiveness of percutaneous PFO closure.

Variable	Lower	Base value	Upper	Reference
Transition probabilities[a]				
Recurrent stroke, annual				
PFO Closure	0.29%	0.36%	0.52%	Kitsios *et al.*[11]
Medical Therapy	1.05%	1.31%	2.53%	Kitsios *et al.*[11]
Moderate severity[b]	0%	30%	100%	
Post-stroke death, annual	3.6%	4.5%	5.4%	±20%
Costs[a]				
PFO closure				
Total cost	£6,644	£6,644	£8,637	+30%
Stroke, 12-month costs				
Minor stroke	£8,224	£10,281	£12,337	±20%
Moderate stroke	£12,889	£16,111	£19,333	±20%
Post-stroke, annual costs				
Minor stroke	£1,862	£2,328	£2,793	±20%
Moderate stroke	£2,918	£3,648	£4,377	±20%
Anti-thrombotic medication, annual				
Aspirin, 75 mg	£4	£5	£6	±20%
Clopidogrel, 75 mg	£32	£40	£48	±20%
Utilities[ab]				
Stable state				
Medical therapy	0.72	0.80	0.88	±10%
PFO closure	0.79	0.88	0.97	±10%
PFO implant, 3-month	0.80	0.84	0.88	±10%
Post-minor stroke				
First 6 months	0.69	0.73	0.77	±5%[7]
Thereafter	0.71	0.75	0.79	±5%[7]
Post-moderate stroke				
First 6 months	0.450	0.50	0.550	±10%[7]
Thereafter	0.558	0.62	0.682	±10%[7]
Dead		0.00		Fixed

[a]Triangular distributions.
[b]One-way sensitivity analyses: moderate stroke severity ranged from 0–100%, Utility values ±5%.

Sensitivity analysis

One-way sensitivity and probabilistic sensitivity analyses (PSA) were performed to assess the robustness of the model and the baseline findings (Table 2). A Tornado diagram of ICER outcomes illustrated one-way sensitivity analysis. PSA was performed using 10,000 Monte Carlo iterative samples. Parameter ranges for recurrent stroke probabilities were based on a review of longitudinal comparative and single arm studies published through 2012[11]. Parameter ranges for stroke cost and post-stroke utility were based on 95% confidence intervals of mean values from the literature[7,24]. Parameters were sampled using triangular distributions for controlled comparisons. When definitive upper or lower bound values were not available, ranges were varied by ±20% of the base values for costs and probabilities[8]. The base case assumption for stroke severity was varied from 0–100% in one-way sensitivity analysis.

Results

Compared with medical therapy alone, PFO closure in the UK sub-population reached cost-effectiveness at 4.2 years (Figure 2).

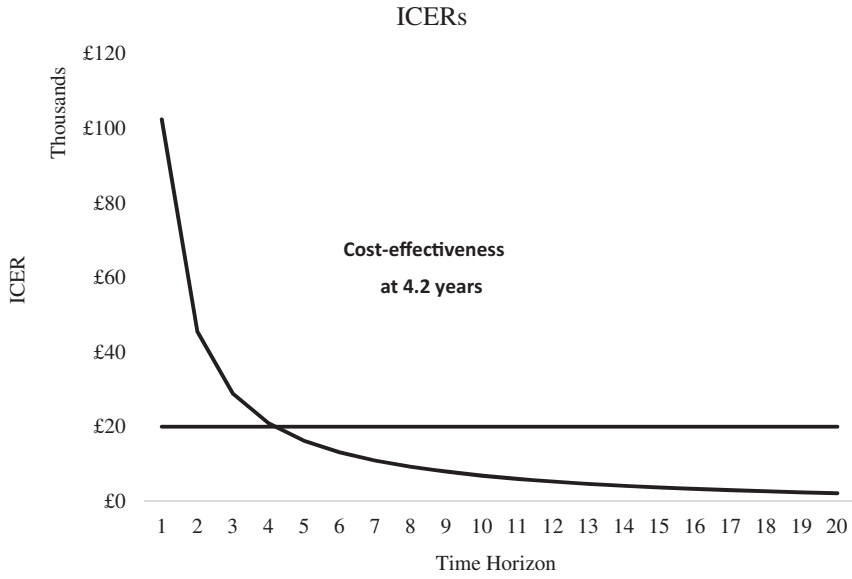

Figure 2. Base case ICERs of percutaneous PFO closure, time horizons 1–20, WTP = £20,000.

Table 3. Base case results of cost-effectiveness of percutaneous PFO closure.

	PFO closure	Medical therapy	Incremental
Outcomes at 4 years			
Total costs	£6,847	£776	£6,071
Total QALYs	3.25	2.96	0.29
ICER			£20,951
Outcomes at 10 years			
Total costs	£7,287	£2,429	£4,858
Total QALYs	7.29	6.59	0.71
ICER			£6,887
Outcomes at 20 years			
Total costs	£8,084	£5,237	£2,846
Total QALYs	12.12	10.80	1.32
ICER			£2,158

At year 4, an average patient in the PFO closure group gained 0.29 QALYs with an increased cost of £6,071 compared to medical management alone, for an ICER of £20,951. The ICER at year 10 was £6,887, 0.71 QALYs gained, with an increased cost of £4,858 (Table 3). The ICER at year 20 was £2,158, 1.32 QALYs gained, with an increased cost of £2,846.

Because cost-effectiveness was reached in less than 10 years, sensitivity analyses results were reported for the relevant 10-year time horizon. One-variable sensitivity analysis using a 10-year time horizon suggested that the most influential factors were utilities of the Stable state for both treatment groups and probability of recurrent stroke in the medical management alone group (Figure 3). ICERs ranged from £4,600–£13,500 as Stable PFO closure utility varied from 0.92–0.84. ICERs ranged from £4,800–£12,000 as Stable medical management utility varied from 0.76–0.84. The highest ICERs from Stable utility sensitivity analyses were well below £20,000. Most of the one-variable sensitivity analyses ICERs were under £10,000.

Using a £20,000 threshold and a 10-year time horizon, probabilistic sensitivity analyses found that PFO closure was cost-effective for 89% of iterations (Figure 4), illustrated by a cost-effectiveness scatterplot (Figure 5).

Discussion

We found that, in the UK sub-population (patients with cryptogenic stroke with atrial septal aneurysm and/or large shunt size and no additional traditional risk factors), PFO closure became cost-effective at 4.2 years. We used the treatment effect from this UK sub-population of the RESPECT trial with these baseline features, which showed a nearly percentage point lower annual probability (0.36% vs 1.31%) of stroke per year for PFO closure plus medical therapy compared to medical therapy alone. This analysis assumed that the AMPLATZER PFO Occluder was the only device used for the PFO closure, since this device has the greatest amount of data supporting effectiveness from randomized clinical trials published to date.

Economic evaluations comparing PFO closure to medical therapy for recurrent stroke prevention have reported encouraging results[32,33]. Using a US perspective and results from short-term clinical trial follow-up, Pickett *et al.*[33] found PFO device closure to be cost-effective compared to medical therapy alone. Although PFO closure had high procedural costs, they were offset by reduced event rates and lower costs of long-term medical treatment, leading to cost-effectiveness at 2.6 years[33]. Our model builds on the analyses published by Pickett *et al.* by assessing cost-effectiveness of PFO closure therapy in the context of the UK healthcare systems. We used UK-specific assumptions for the patient population, costs, and utilities. To evaluate PFO closure technology, NHS England created an observational registry using a Commissioning through Evaluation (CtE) program[34]. Moreover, the NHS has funded a survey of current PFO closure practices among cardiologists, stroke physicians, and neurologists in the UK[18]. The resulting publication reported that 89% of specialists indicated that PFO closure should be considered in selected patients with cryptogenic stroke[18]. The anatomical variations of PFO are important, but there is no solid evidence of an association between anatomical features and high risk of stroke recurrence. The focus of this study

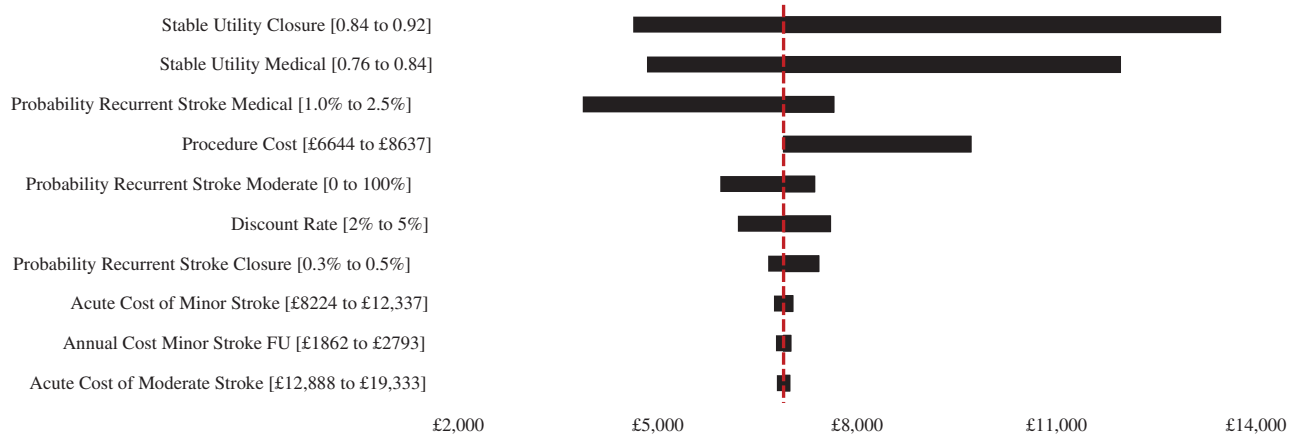

Figure 3. One-variable sensitivity analysis for cost-effectiveness of percutaneous PFO closure, 10-year time horizon.

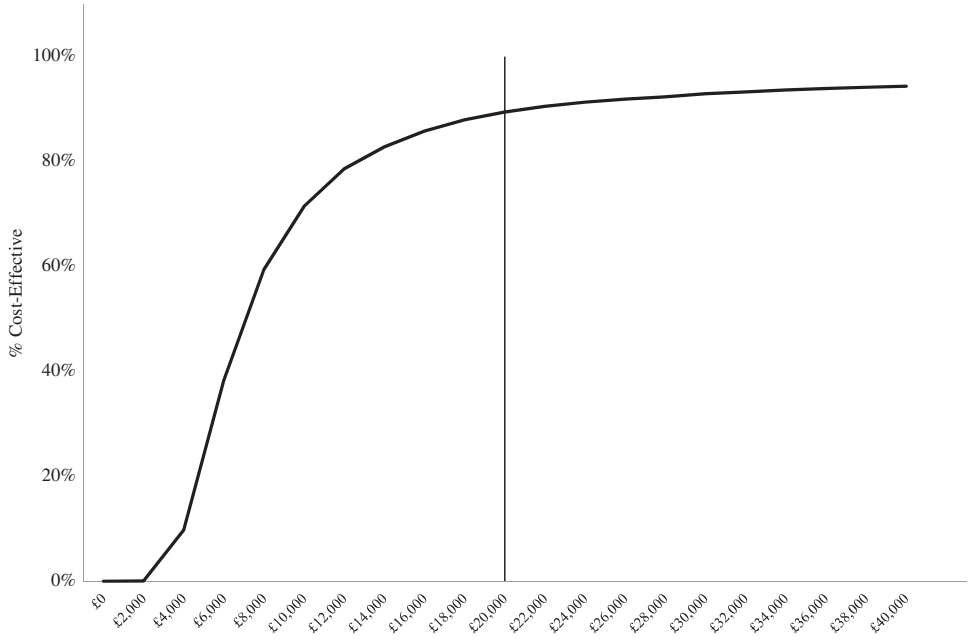

Figure 4. Acceptability curve for cost-effectiveness of percutaneous PFO closure, 10-year time horizon.

was a comparison of percutaneous PFO closure plus medical therapy to medical therapy alone for PFO patients who had a cryptogenic stroke and a large degree of right-to-left shunt or atrial septal aneurysm in the UK real-world practice according to the survey results—the UK sub-population.

It is noteworthy that the reduction in stroke recurrence observed in the UK sub-population of the RESPECT trial was similar to the one reported by the CLOSE trial. The CLOSE trial[12] reported approximately the same absolute difference—0% for PFO closure plus medical therapy vs 1% for medical therapy alone—although it employed a variety of PFO closure devices (with the AMPLATZER device being most common)[12]. This similarity in the treatment effect size in the UK sub-population of the RESPECT trial and the CLOSE trial supports generalizability of the model results.

To assess internal validity of our model, we also performed a cost-effectiveness analysis on the entire RESPECT trial using the Intent-to-Treat cohort[35]. The relative risk reduction was slightly lower, with the probability of recurrent ischemic stroke at 1.07 per 100 patient years in the medical therapy vs 0.58 in the PFO closure group. As expected, ICERs in the entire RESPECT cohort were higher at £20,952, £6,887, £2,158 at 4, 10, and 20 years, respectively. Compared with medical therapy alone, PFO closure reached cost-effectiveness at 4.5 years.

Higher health-related utility due to the avoidance of recurrent stroke with decremental impact on QoL was an important driver of cost-effectiveness in the current study. Consequences of stroke, especially recurrent ones, can be devastating, not only physically, but also economically or psychologically. Studies reported that stroke has a tremendous negative impact on QoL, as well as daily functioning[32]. Hence, recurrent strokes exacerbate the negative impact in all of the health-related QoL dimensions. Another significant contributor was utility improvement due to reduced psychological distress regarding risk of recurrent paradoxical stroke after the PFO closure procedure[36]. Our base case assumption was that that PFO closure would improve QoL by 10%, from

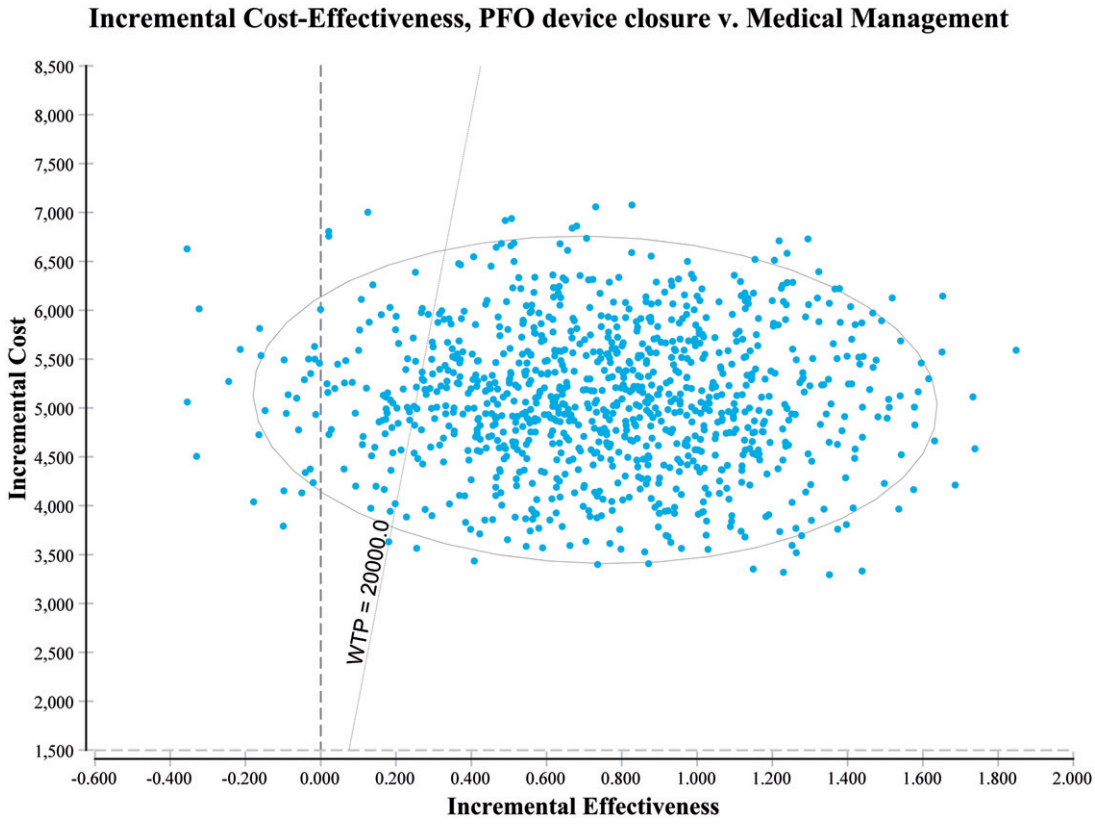

Figure 5. Cost-effectiveness plane of percutaneous PFO closure, 10-year time horizon.

0.80 to 0.88. In one-way sensitivity analysis, we tested a more modest 5% improvement, from 0.80 to 0.84. The 10-year ICER increased to £13,500, but remained cost-effective.

The relatively young age of the patients and their lack of typical cardiovascular risk factors make this analysis especially critical for public health, since the clinical, economical, and emotional burdens of stroke are likely to be incurred by the patients, healthcare system, and the society for a long-life expectancy of the stroke survivors.

We believe that the model reflects the real-world population in the UK healthcare system relatively well, because the patient population, the medical regiments, and costs are reflective of the current practice in the UK. However, this study has limitations.

First, post-stroke utility values in this study were based on a study of a UK population in which the patient cohort was older, on average, than the patient cohort in our model[7]. The impact of stroke on QoL in younger patients may be more profound compared with older patients. Notably, loss of personal and national income from the inability to work is frequent in young and middle-aged stroke patients, and less common among older, often retired, stroke patients.

Second, medical therapy can consist of a combination of generic with non-generic medications in both medical therapy alone and PFO closure groups. For the purpose of this analysis, we conservatively assumed a relatively simple medication regimen with cost reflecting the generics available in the UK.

Third, this analysis assumed that all patients were implanted with the AMPLATZER PFO Occluder. Recent studies have shown that PFO closure devices have different safety profiles, which could be better or worse than the AMPLATZER PFO Occluder. More severe and/or frequent device- and procedure-related complications and lower rates of successful PFO closure are likely to increase the cost of the PFO closure treatment, which in turn may reduce cost-effectiveness of this therapy.

Fourth, this analysis only examined direct healthcare costs. Stroke patients also incur substantial costs related to informal caregiving and lost productivity. Accordingly, this analysis is conservative with regard to the total cost-effectiveness of intervention.

Fifth, mortality rate post-stroke was based on an older population than our modeled cohort, and also without a history of stroke. Data on long-term mortality of young post-cryptogenic stroke patients is limited. RESPECT[13] trial data is not reliable, because there were only 25 strokes, and patient follow-up was 6 years post-enrollment, not post-stroke. The Li *et al.*[21] study offers the most robust mortality post-cryptogenic stroke information, because of the sample size and the length of follow-up. Moreover, our sensitivity analysis of post-stroke mortality varied by ±20% resulted in very little change in the 10-year ICER (£6,866 and £6,909 vs base case £6,887). In addition, we ran a scenario with post-stroke mortality equal to the background mortality at age 46, an annual mortality rate of 0.2%. Results of that scenario were very similar to the base case: ICERs at 4, 10, and 20 years were £21,080, £7,007, and £1,865; cost-effectiveness was reached at 4.2 years. Post-stroke mortality may have a low impact on results, because the number of patients with stroke is so low,

and because post-stroke mortality affects cost-effectiveness in two directions: post-stroke patients that live longer accumulate more utility, yet they accumulate additional post-stoke treatment costs.

Finally, this analysis didn't assess the potential impact of patient's age. As patients age they are likely to develop cardiovascular risk factors that could compete with the risk of PFO mediated strokes, which could diminish the cost-effectiveness of PFO closure in older patients. However, in the real-world setting this effect is likely to be minimal, due to the relatively young age of PFO closure patients, and a narrow age range reported by the RESPECT trial with a mean and standard deviation of 45.9 ± 9.9.

Conclusions

Considering the UK healthcare system perspective, percutaneous PFO closure using the AMPLATZER PFO Occluder in patients with cryptogenic ischemic stroke, PFO, and additional high risk anatomic features is a cost-effective secondary stroke prevention strategy compared to medical therapy alone. Its cost-effectiveness was driven by reduced recurrent strokes and improved health-related QoL.

Transparency

Declaration of funding

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Declaration of financial/other relationships

DT has worked as a Neurology Executive member and a consultant on educational issues and has received contracted hourly payments from Abbott. MT has worked as a consultant on education and procedure proctoring and has received contracted hourly payments from Abbott. DT, DM, JC, LM, RS, and JLS have worked as Trial Steering Committee members, advising on rigorous trial design and conduct, and have received contracted hourly payments from Abbott. MK and NYG are employees of Abbott, Inc. Peer reviewers on this manuscript have received an honorarium from JME for their review work, but have no other relevant financial relationships to disclose.

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