Cost-Effectiveness Analysis of Alternative Strategies for the Management of Patients with Cryptogenic Stroke and Patent Foramen Ovale

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SUMMARY

Background
Patent foramen ovale (PFO) has been associated with cryptogenic stroke (CS). There are still some controversies about the best treatment to prevent recurrences in patients with CS and PFO. Our region lacks cost-utility analysis of the management of these patients.

Objective
To construct a decision model for the management of patients with CS and PFO and to establish the cost-utility ratio of three alternative strategies.

Material and Methods
We conducted a cost-utility analysis based on a decision tree with a time horizon of 4 years considering three strategies: aspirin (ASA), anticoagulants (AC) or percutaneous device closure of the PFO. The benefits were expressed in QALYs. A payment threshold of ARS $28,000 was established and a sensitivity analysis was performed.

Results
Anticoagulants were more expensive compared to ASA (additional cost of ARS $1,315) and produced less benefits (incremental (QALY –0.063). Percutaneous device closure had an additional cost of ARS $89,876 per QALY gained compared to ASA. This cost exceeds the predetermined payment threshold. After performing the sensitivity analysis, ASA remained as the strategy with the best cost-utility ratio; however, when the probability of recurrences with this drug increases to 35%, anticoagulants present an incremental cost-utility ratio of ARS $1.356/QALY.

Conclusions
According to this model, in patients with CS and PFO, ASA would be the strategy with the best cost-utility ratio in our environment unless recurrences develop; in this case the use of anticoagulants would be more appropriate.

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Key words > Patent foramen oval - Cryptogenic stroke - Therapeutics - Economic evaluation - Cost-utility- Model

Abbreviations >

ASA:	Aspirin	**TIA:**	Transient ischemic attack
ACCP:	American College of Chest Physicians	**RCT:**	Randomized clinical trial
AC:	Anticoagulation	**PFO:**	Patent foramen ovale
Stroke (CVA) :	Stroke (Cerebrovascular accident)	**QALYs:**	Quality adjusted life years
AHA/ASA:	American Heart Association/American Stroke Association	**CS:**	Cryptogenic stroke

INTRODUCTION
Stroke (CVA) is the third cause of death and the leading cause of disability worldwide. (1) Most strokes are ischemic. However, the cause in about 25-40% of them remains unclear despite its systematic diagnostic research, and they are called cryptogenic

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strokes (CS). (2-5) Several studies show an association between patent foramen ovale (PFO) and CS. (6-9) The presence of recurrent stroke in patients with PFO has also been documented. (10) At present, there are three alternative treatments for PFO patients who had isquemic stroke: aspirin (ASA), anticoagulation (AC), and percutaneous device closure. The efficacy of these strategies has been compared in observational studies, and several randomized clinical trials (RCT) are currently in progress. (11-16) While the data have not been revealed, the sponsor of the CLOSURE trial has recently announced that outcomes of the medical treatment with percutaneous closure device have been negative. (17) Besides, the costs of these alternatives are very different, and in our country there are no cost-effectiveness studies that have evaluated this issue.

This work was carried out to develop a decision model for the management of patients with cryptogenic stroke and patent foramen ovale, and to establish the cost-utility ratio of three alternative strategies.

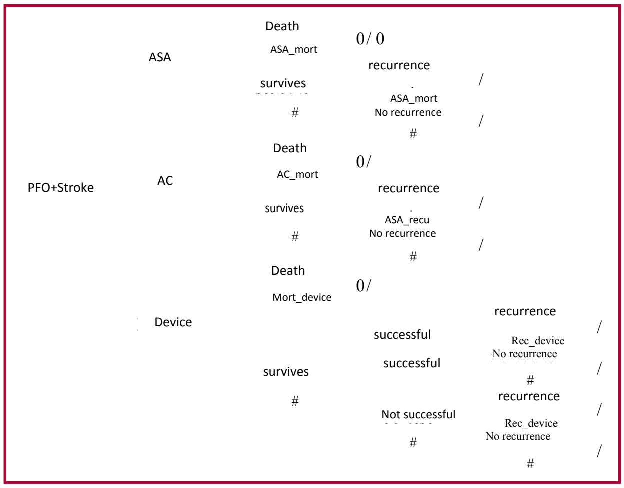

Fig. 1. Decision tree.

MATERIAL AND METHODS

A complete cost-utility analysis was conducted. The model was based on a decision tree that included costs and utilities of three alternative strategies (Figure 1). Costs were expressed in Argentine pesos, and utilities in QUALYs (Quality adjusted life years). Data were taken from literature and from experts' opinions. The analysis was performed with the DATA Tree program.

Definition of base case and model assumptions

The base case was defined as a hypothetic cohort of patients aged 50 with a history of stroke and PFO diagnosed by bubble-contrast transesophageal echocardiography, in the absence of vascular disease, other sources of cardioembolism, prothrombolic factors, and in the presence of sinus rhythm. The event was defined at the occurrence of stroke or transient ischemic attack (TIA) with a 4 year time horizon. Recurrence was considered to occur in the first year, so neither costs nor QUALYs associated with it were discounted. TIA utility ratio was similar to that of 'minor' stroke reported in the literature. (18) Neither costs nor QALYs were discounted in the first year (it was considered that the cost was at the beginning of the period); therefore, they were discounted starting from the second year. No complications in any branch were considered to simplify the model.

When the data were expressed in more than one year in the literaure, it was considered that the rate of events was similar in each yearly period.

Decision rules and sensitivity analysis

When compared with another strategy, a "dominated strategy" was the one that conferred higher cost and lower benefit ratios, whereas a "dominating strategy" was that which presented lower cost and higher benefit ratios. When the strategy showed higher benefit and lower cost, or lower benefit and lower cost, a payment threshold was used to make the decision. The willingness to pay that was set to accept an intervention as 'useful-cost' was 1 GDP per capita, equivalent to an incremental cost-utility ratio of ARS $28,000 for each extra QALY gained. A deterministic sensitivity analysis was carried out to explore the uncertaintiy of the model outcomes. A tornado diagram was performed to identify the variables with greatest influence on the outcomes. Once these variables were identified, the result was evaluated again by analyzing the scenario, that is, with the lower and upper ranges of the central estimation.

Perspective

The perspective of the financer (Health Insurance Plan) was used.

Alternative strategies

- Aspirin treatment: Patients were treated with aspirin 300 mg/day, they visited their cardiologist twice a year, and no screenings were performed.
- Acenocumarol treatment: Patients were treated with acenocumarol as determined by lab tests. They visited their cardiologist twice a year, and their hematologist, once a month. No screenings were performed, except for the monthly anticoagulation monitoring.
- Percutaneous device closure of PFO: After the intervention, patients were treated with aspirin 300 mg/day. They were controlled by the cardiologist every 3 months.

Probabilities utilized

The probabilities used (point estimate), as well as the sensitivity analsysis range are shown in Table 1. Data were taken from the literature and from the experts' opinions. (11)

Benefits utilized

QALYs for stroke were obtained from the review by Post et al. (18) Since the recurrence endpoint was stroke or TIA, an average between the mean QALY of such revision for 'minor' and 'major' stroke was obtained. (18) Such values were changed for the sensitivity analysis, taking the higher QALY (minor stroke) and lower QALY (major stroke). A 3% discount was obtained (a 0-10% range was used for the sensitivity analysis). A zero QALY value was considered for mortality rate. Utilities elicited from treatment with antiplatelet agents or anticoagulants, or from the device closure were obtained by the authors of the work with the Visual Analogue Scale. Benefits expressed in QALYs were modified by ± 10% for the sensitivity analysis. Utilities are shown in Table 1.

Variable	Central estimation	Range
Probabilities (%)		
Aspirin mortality rate	3.9	3-5
Anticoagulation mortality rate	2.5	1-4
Device closure mortality rate	0.7	0.2-1.3
Device closure success rate	83	75-95
Recurrence with aspirin	25.Re4	15-35
Recurrence with anticoagulation	19.3	15-25
Recurrence after device closure		
(unsuccessful)	7.8	4-12
Recurrence after device closure (successful)	6.4	2-10
Costs (ARS $)		
Annual cost of aspirin therapy	196	171-221
Annual cost of anticoagulation therapy	740	550-900
Annual cost of device closure	34,000	30,000-38,000
Cost of recurrence	12,987	10,000-17,000
QALYS		
Minor stroke	0.72	± 10%
Major stroke	0.41	± 10%
Minor and major stroke	0.57	± 10%
ASA therapy	0.98	± 10%
AC therapy	0.92	± 10%
Treatment with closure device	0.95	± 10%

Probabilities expressed in percentages, costs expressed in pesos, and utilities expressed in QALYs.

Table 1. Probabilities, costs and QALYs utilized. Central estimation and range for sensitivity analysis

Costs utilized

Costs were expressed in Argentine pesos (ARS), and the currency exchange was 1 dollar = 4 pesos in October 2010. To estimate the costs, only medical direct costs were considered; non-medical direct costs, indirect costs, or productivity costs were not taken into account.

Medication costs were obtained from the pharmacy price list of the Hospital Italiano. To elicit the mean cost per stroke (recurrence), it was found that one third of the patients presented low costs (ARS $9,000), since they only required hospitalization, imaging studies, anticoagulant and/or antiplatelet therapy, and post-stroke rehab through kinesiology; another third of the patients required interventions with longer hospitalization periods and involved digital angiographies at a mean cost of ARS $12,000; finally, a third group required open surgeries or percutaneous interventions at a mean cost of ARS $18,000. This represents an estimated mean cost of around ARS $12,987 per stroke. (19) Table 1 shows in detail the main costs used, as well as the sensitivity analysis range.

Discount

A 3% discount rate was used both for costs and benefits. In the sensitivity analysis, a range between 0% and 10% was considered.

RESULTS

Acenocumarol treatment produced an incremental cost of ARS $1,315 with respect to ASA, but benefits were low (incremental QALY –0.063). Therefore, anticoagulation strategy is considered to be dominated by aspirin (Figure 2 & Table 2).

Compared with aspirin treatment, percutaneous device closure showed an incremental cost of ARS $32,261 and an incremental benefit of 0.359 QALY; it represents an incremental cost-utility ratio of ARS $89,876 per each extra QALY gained.

Variables detected by the "tornado diagram" and "submitted" to sensitivity analysis were the following: 1) recurrence with aspirin, 2) cost of recurrence, 3) QALYs, 4) discount, and 5) cost of aspirin (Figure 3).

After performing the sensitivity analysis, when the probability of recurrence with ASA was reduced to 15%, anticoagulation remained domained by ASA, and the incremental cost-utility ratio of the device over ASA was ARS $169,742/QALY. However, when the probability of recurrence with ASA increased to 35%, anticoagulants presented an incremental cost-utility ratio of ARS $1,356/QALY, and ARS $73,403/QALY for devices, with respect to ASA in both cases.

When the recurrence cost was reduced to ARS $10,000, anticoagulants remained dominated by ASA, and the incremental cost-utility ratio for the device over ASA was ARS $91,351/QALY. When the recurrence cost increased to ARS $17,000, AC remained dominated by ASA, and the incremental cost-utility ratio for the device over ASA was ARS $87,892/QALY.

When QALY variable was changed based on the lower range of 0.9, anticoagulation remained dominated by ASA, and the incremental cost-utility ratio for the device compared with that drug was ARS $99,861/QALY. When QALY variable was changed based on the upper range of 1.1 QALY, AC remained dominated by ASA, and the incremental cost-utility ratio for the device compared with that drug was ARS $81,705/QALY.

When the discount rate was changed to 0%, AC remained dominated by ASA and the incremental cost-utility ratio for the device compared with ASA was ARS $85,545/QALY. When the discount rate was changed to 10%, AC remained dominated by ASA and the incremental cost-utility ratio for the device compared with ASA was ARS $99,967/QALY.

When the cost of ASA was reduced to ARS $171, AC remained dominated by ASA, and the incremental cost-utility ratio for the device over this drug was ARS $89,867/QALY. When the cost of ASA increased to ARS $221, AC remained dominated by ASA, and the incremental cost-utility ratio for the device over this drug was ARS $89,884/QALY.

DISCUSSION

Today, the number of publications about the cost-effectiveness relationship in cardiology is growing. (20) However, no studies on the treatment cost-effectiveness for patients with PFO in secondary prevention have been carried out.

While RCT are being carried out with some difficulties in the enrollment of participants (12-16), decisions have to be made about these patients with the available information regarding the effectiveness, safety, and cost of the different strategies. Both the AHA/ASA (American Heart Association/American Stroke Association) (21) and the ACCP (American College of Chest Physicians) (22) guidelines recommend antiplatelet therapy for patients with ischemic stroke or TIA and PFO (AHA/ASA Class IIa, Level of Evidence B; ACCP grade 1A), unless there are indications for anticoagulation due to other associated conditions (atrial fibrillation, hypercoagulable state, deep vein thrombosis, AHA/ASA Class IIa, Level of Evidence C; ACCP grade 1C). These same guidelines for secondary prevention of stroke state that "there are insufficient data to provide a recommendation on percutaneous closure of PFO in patients with a first episode of stroke, although the procedure may be applied in recurrent stroke, despite optimal medical treatment (Class IIb, Level of Evidence C)". (21) Recently, an interesting controversy about percutaneous closure in patients with stroke and PFO has been published in the Argentine Journal of Cardiology, (23) in which both authors agree on the need to wait for the outcomes of randomized studies currently in progress to draw more definitive conclusions. The cost-utility relationship might help make decisions in certain scenarios, especially when resources are limited, and there is also a marginal benefit of a treatment with respect to another at the expense of substantially increased costs.

This model shows that, according to the payment threshold of ARS $28,000/QALY recommended by the World Bank for economies like ours in Argentina, (24) the device strategy resulted in cost-ineffective. These results were unchanged after the sensitivity analysis; furthermore, the device strategy would not be cost-effective either if we considered a less demanding payment threshold, such as 3 GDP per capita (eg. ARS $84.000). Anticoagulation strategy has been dominated by ASA, because AC was more expensive and less effective. These results were maintained after the sensitivity analysis, except when the probability of recurrence with ASA increased to 35%. In those cases,

Fig. 2. Diagram of the cost-utility ratio (axe y: incremental cost; axe x: incremental effectiveness). It can be observed that the anticoagulation strategy is dominated by ASA. The device strategy's cost and effectiveness is higher than for ASA, but the slope representing the cost-utility ratio is very "steep" (continuous line). It is also observed how the slope (dotted line) corresponding to a hypothetical payment threshold of ARS $28,000/QALY would also be steeped.

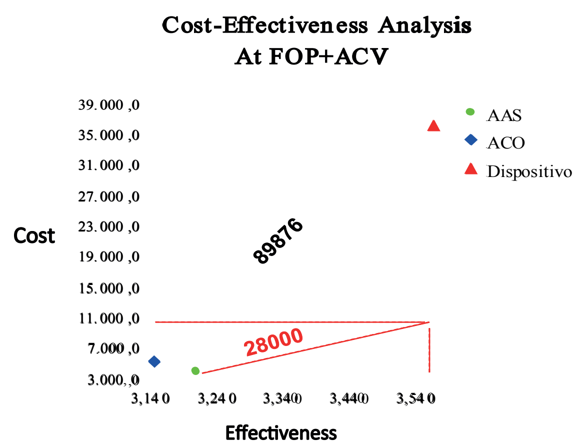

Table 2. Incremental cost-utility ratio

Strategy	Cost	Incremental cost	Benefit (QALYs)	Incremental benefit	Mean C-U	Incremental C-U
ASA	3,891	–	3.212	–	1,211	–
AC	5,206	1,315	3.149	–0.063	1,653	DOMINATED
Device	36,152	32,261	3.571	0.359	10,124	89,876

C-U: Cost-Utility.

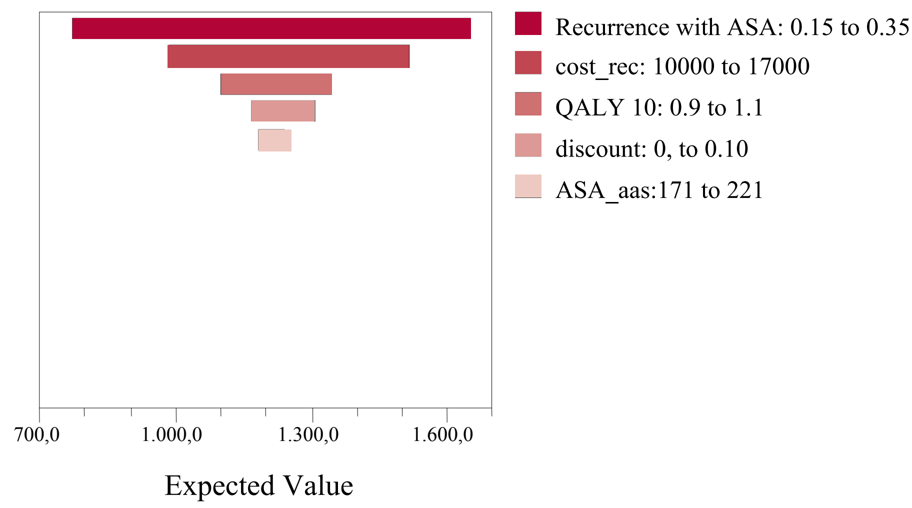

Fig. 3. This chart shows in decreasing order the influence the following variables have on the expected value: Recurrence with aspirin; cost of recurrence; QALYs; discount; and aspirin cost. It also shows the range of each of them used for the sensitivity analysis.

anticoagulant therapy is the best strategy, because –compared with ASA– it has an incremental cost-utility ratio of only ARS $1,356 per each extra QALY gained (i.e. far below the predetermined payment threshold).

Limitations

The limitations of this study are probably related to the methodology inherent to model-based economic evaluations. The assumptions and simplicity of the model might undermine the validity of this study. More complex models like those of Markov, and probabilistic simulation sensitivity analyses might show how the incremental cost-utility ratio behaves according to the changes in the payment threshold. (25) As commented above, probabilities, costs, and QUALYs of the complications of each of the alternatives were not included. It would be difficult to determine the influence of each of the complications on the model due to its frequency and severity, and its possible implications both on quality of life and costs. But it is also worth mentioning that each of the alternatives may be associated with severe complications, such as allergies, major bleeding, device embolization, and cardiac tamponade.

Besides, this study did not analyze the cost-utility relationship of the strategies in the different subgroups most likely to have recurrent events (for instance, atrial septum aneurysm, large foramen ovale, and thrombophilia); (10, 26) therefore, it is uncertain whether the cost-utility ratio of ASA is higher than other therapeutic alternatives for these patients in particular.

Finally, regarding the external validity of this study, caution should be taken with extrapolation of results to other countries with different economies, since the differences in the costs of interventions, variations in payment threshold, and preferences of doctors and patients might affect the conclusions of this model.

CONCLUSIONS

According to this model, ASA would be the strategy with the best cost-utility ratio for patients with cryptogenic stroke and patent foramen ovale in our environment, unless recurrence of events is substantially higher with this drug, in which case the use of anticoagulants would be appropriate.

RESUMEN

Análisis de costo-efectividad de estrategias alternativas en el manejo de pacientes con accidente cerebrovascular criptogénico y foramen oval permeable

Introducción

El foramen oval permeable (FOP) se ha asociado con el accidente cerebrovascular criptogénico (ACVC). El mejor tratamiento para evitar la recidiva en pacientes con ACVC y FOP es controversial. No existen datos de costo-utilidad en nuestra región para el manejo de estos pacientes.

Objetivo

Construir un modelo de decisión para el manejo de pacientes con ACVC y FOP y establecer la relación costo-utilidad de tres estrategias alternativas.

Material y métodos

Se realizó un análisis de costo-utilidad basado en un árbol de decisión con un horizonte temporal de 4 años considerando tres estrategias: aspirina (AAS), anticoagulación (ACO) o cierre percutáneo del FOP con dispositivo. Los beneficios se expresaron en QALYs. Se fijó un umbral de pago de $28.000 argentinos y se realizó un análisis de sensibilidad.

Resultados

En comparación con la AAS, la anticoagulación fue más costosa ($1.315 adicionales) y generó menos beneficios (QALY incremental –0,063). El cierre con

dispositivo comparado con el tratamiento con AAS costaría $89.876 adicionales por QALY ganado. Dicho monto supera el umbral de pago predeterminado. Luego del análisis de sensibilidad, la AAS se mantuvo como la estrategia con mejor relación costo-utilidad, salvo cuando la probabilidad de recidiva con esta droga aumenta al 35%, en donde la anticoagulación presenta una tasa de costo-utilidad incremental de $1.356/QALY.

Conclusiones

De acuerdo con este modelo, para pacientes con ACVC y FOP, la AAS sería la estrategia con mejor relación costo-utilidad en nuestro medio, salvo cuando la probabilidad de eventos se eleva sustancialmente, en cuyo caso sería apropiado el uso de anticoagulantes.

Palabras clave > Foramen oval permeable - Accidente cerebrovascular criptogénico - Terapéu tica - Evaluación económica - Costo-utili dad - Modelo

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Declaration of conflict of interest
The authors declare they do not have a conflict of interest.