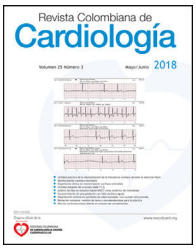
Rev Colomb Cardiol. 2019;26(2):70–77

Asociación SOCIEDAD COLOMBIANA DE CARDIOLOGÍA & CIRUGÍA CARDIOVASCULAR

Revista Colombiana de Cardiología

www.elsevier.es/revcolcar



ADULT CARDIOLOGY – ORIGINAL ARTICLE

Cost-effectiveness of new oral anticoagulants and warfarin in atrial fibrillation from adverse events perspective

José A. Mendoza[a,*], **Federico A. Silva**[b], **Lady M. Rangel**[b]

[a] *Grupo de Ciencias Neurovasculares, Instituto Neurológico, Hospital Internacional, Fundación Cardiovascular de Colombia, Floridablanca, Colombia*
[b] *Universidad Industrial de Santander. Bucaramanga, Colombia*

Received 17 March 2017; accepted 9 October 2018
Available online 9 April 2019

KEYWORDS
Economic evaluation;
Stroke;
Warfarin;
Dabigatran;
Rivaroxaban;
Anticoagulants

Abstract
Objective: new oral anticoagulants (apixaban, dabigatran and rivaroxaban) are the newest advance for stroke's risk reduction in atrial fibrillation. These are as effective as warfarin in preventing stroke/systemic embolism, but exists heterogenic outcomes as gastrointestinal hemorrhage, mortality reduction, minor and major haemorrhage (adverse events). Despite of this, there is a lack of cost-effectiveness models focused on adverse events.
Methods: a cost-effectiveness analysis with a third payer perspective, interventions included were apixaban, dabigatran, warfarin and rivaroxaban. Discount rate of 3%, and 10 years of temporal horizon. The Markov model is an international, validated, and modified to assess better adverse events. Major assumptions, patients with mild and moderate stroke returns to oral anticoagulation, patients with moderate and severe hemorrhage do not returns to oral anticoagulation. Probabilities and QALYs, taken from a cost-effectiveness analysis published. Costs, information from a cohort of stroke patients. Software, TreeAge pro™ and Excel™.
Results: overall results, 1.48 QALYs, $17 916 USD for apixaban, 1.49 QALYs, $18 122 USD for dabigatran, 1.32 QALYs, $21 966 USD for warfarin and 1.24 QALYs, $24 547 USD for rivaroxaban. The ICER for apixaban compared to dabigatran was $12 988 USD. Negative ICER for warfarin and rivaroxaban, shows that are dominated alternatives (less benefits and more costs). Apixaban is cost-effective at 70% and dabigatran at 30% of iterations in the probabilistic sensitivity analysis.

Abbreviations: AF, atrial fibrillation; ICH, intracranial hemorrhage; GIH, gastrointestinal hemorrhage; CEA, cost-effectiveness analysis; ICER, incremental cost-effectiveness analysis.
Abreviaturas: AF, fibrilación auricular; ICH, hemorragia intracraneal; GIH, hemorragia gastrointestinal; CEA, Análisis de costo-efectividad; ICER, radio costo-efectividad incremental.

* Corresponding author.
E-mail address: jmendoza45@msn.com (J.A. Mendoza).

https://doi.org/10.1016/j.rccar.2018.10.011

Conclusions: apixaban and dabigatran are cost-effective alternatives, apixaban is the most cost-effective alternative from adverse events perspective. Warfarin shows better results than rivaroxaban to prevent stroke in atrial fibrillation from adverse events perspective.

PALABRAS CLAVE
Evaluación económica;
Ictus;
Warfarina;
Dabigatrán;
Rivaroxabán;
Anticoagulantes

Análisis de costo-efectividad de los nuevos anticoagulantes orales y la warfarina en fibrilación auricular desde la perspectiva de los eventos adversos

Resumen
Introducción: los nuevos anticoagulantes orales (apixabán, dabigatrán y rivaroxabán) son el avance más reciente para la reducción del riesgo de accidente cerebrovascular en la fibrilación auricular. Estos son tan efectivos como la warfarina en la prevención del accidente cerebrovascular/embolia sistémica, pero existen resultados heterogéneos como hemorragia gastrointestinal, reducción de la mortalidad y hemorragia menor y mayor (eventos adversos). Pese a ello, se carece de modelos de costo-efectividad enfocados en eventos adversos.
Materiales y métodos: se hizo un análisis de costo-efectividad con una perspectiva de tercer pagador, en el que se incluyeron intervenciones como apixabán, dabigatrán, warfarina y rivaroxabán. La tasa de descuento fue del 3% y 10 años de horizonte temporal. El modelo de Markov es internacional, validado y modificado para evaluar mejor eventos adversos. Las principales suposiciones, los pacientes con accidente cerebrovascular leve y moderado vuelven a la anticoagulación oral, los pacientes con hemorragia moderada y grave no regresan a la anticoagulación oral. Probabilidades y AVAC, tomados de un análisis de costo-efectividad publicado. Los costos, información de una cohorte de pacientes con accidente cerebrovascular. Software, TreeAge pro y Excel.
Resultados: resultados generales, 1.48 QALYs, $ 17 916 USD para apixabán, 1.49 QALYs, $ 18 122USD para dabigatrán, 1.32 QALYs, $ 21 966 USD para warfarina y 1.24 QALYs, $ 24 547 USD para rivaroxabán. El ICER para apixabán en comparación con dabigatrán fue de $ 12 988 USD. El ICER negativo para warfarina y rivaroxabán muestra que son alternativas dominadas (menos beneficios y más costos). Apixabán es rentable en 70% y dabigatrán en 30% de las iteraciones en el análisis de sensibilidad probabilístico.
Conclusión: apixabán y dabigatrán son costo-efectivos; apixabán es la alternativa más costo-efectiva desde la perspectiva de los eventos adversos. Warfarina mostró mejores resultados que rivaroxabán para prevenir accidentes cerebrovasculares en fibrilación auricular desde la perspectiva de los eventos adversos.

Introduction

New oral anticoagulants (apixaban, dabigatran and rivaroxaban) are the latest advance in atrial fibrillation (AF). Some of them are effective as warfarin, reducing stroke/systemic embolism (RR 0.78 95% CI 0.67-0.92) and intracranial hemorrhage (ICH) (RR 0.49 95% CI 0.36-0.66)[1]. But exists heterogeneous outcomes as in gastrointestinal hemorrhage (GIH)[2], mortality reduction, minor and major hemorrhage[3–5]. Moreover, exist differences in stroke and ICH rates between them and increase of GIH compared with warfarin. These heterogeneous outcomes (especially in adverse events), higher drug cost yield us to propose —an improvement on calculation of adverse events in economic evaluations of new oral anticoagulants.

Economic evaluations as cost-effectiveness analysis (CEA) compares the relative cost and outcomes of two or more courses of action, in health care is widely used for evaluation of efficiency in drugs and others health care technologies to offer the maximum benefit of available funds[6]; a study by Harvard university found that a double life years could be saving if resources were allocated by cost-effective interventions[7]. Several CEA for new oral anticoagulants have been published, a systematic review of the literature reported incremental cost-effective ratios (ICER) of 20 426 USD ± 19 653 USD for dabigatran 150, $13 834 USD ± 3 885 USD for apixaban and $20 884 USD ± 13 959 USD for rivaroxaban[8]. Two CEA in oral anticoagulation in Colombia showed ICER's of $ 7 846 USD (COP/USD = 2 954, 24 august 2018) for dabigatran 150[9], and $44 524 USD for

apixaban, $28 796 USD for dabigatran and $26 340 USD for rivaroxaban[10].

Most of published CEA differs on the Markov model's structure, but are similar in lacking of more specific adverse events (AE) calculations; a systematic review found that the current modelling assumptions may restrict the understanding of the true impact of AE in CEA of antineoplastic drugs[11], however, for oral anticoagulation this impact is unknown, despite the hemorrhage events are almost two times more than ischemic stroke in pivotal clinical trials[3–5]. The assessment of hemorrhage localization are important due to cost of treatment, for example, the treatment cost of mild upper GIH, severe lower GIH; mild intraparenchymal ICH and severe subdural ICH differs. We propose a CEA in oral anticoagulation in atrial fibrillation in Colombia with the improve on hemorrhage events assessment by localization of intracranial hemorrhage and gastrointestinal hemorrhage, using an international validated Markov model and costs data from a cardiovascular hospital in Colombia, with the aim of identify the most efficient alternative in oral anticoagulation.

Methods

Several Markov models in anticoagulation are described in the literature, for the study we used the Harrington's model as a base from which we modified ICH and GIH to classify events by localization. Four treatment strategies and their associated outcomes were assessed: warfarin (INR 2-3), dabigatran (150 mg twice daily), apixaban (5 mg twice daily), and rivaroxaban (20 mg once daily). The hypothetical cohort of patients with AF, and same characteristics as included in pivotal clinical trials. For this model rate of adherence and drug compliance were assumed the same across of the treatments. The Markov model was designed to move between health states of 1 month cycles for 10 years or until death. Cost-effective therapies were selected using a willingness-to-pay (WTP) threshold of $9 000 USD per quality-adjusted life-year (QALY) gained (approximately 3 times *per capita* gross domestic product) and 3% discount rate. Model's calculations and sensitivity analysis were made using TreeAge pro®.

Model structure

The model inputs of events were taken from literature. The aim was to simulate a cohort of patients with AF that has the similar adherence rate between drugs. It was used major probabilities as risk of stroke, ICH, GIH and other hemorrhage; other bleeding included retroperitoneal hemorrhage, epistaxis, and urinary tract hemorrhage[12]. Events risks calculations of new oral anticoagulants (NOAC) were based on information of pivotal clinical trials (ARISTOTLE, RE-LY, and ROCKET-AF); warfarin probabilities were calculated from pooled clinical trials results. Distribution of stroke rate severity was the same for NOAC and warfarin; it was extracted from Leigh's et al study[13]. Distribution of intracerebral, subdural (intracranial), upper, and lower (gastrointestinal) hemorrhage was taken from economic model of Leigh et al.

For the assessment of a more realistic model in oral anticoagulation, it was used information from a cohort of stroke in a cardiovascular hospital, which was useful to know the physician's believe of hemorrhage and its attitude to restart oral anticoagulation after a major hemorrhage; from this, our model excluded patients with moderate or severe GIH, all the ICH, and moderate stroke and severe stroke, this last one is not consider an adverse event for oral anticoagulation but there are a risk of hemorrhagic transformation of stroke.

Utilities

There is a lack of calculation for QALY's utilities in Colombia. Exists literature descriptions of the baseline utility of a patient with AF in oral anticoagulation treatment, disutilities for stroke (mild, moderate, and severe), intracranial haemorrhage (mild and severe), gastrointestinal haemorrhage (mild, moderate, and severe), other hemorrhage was used from US information.

Costs

Events costs were estimated from information of a cohort of patients with stroke in the Fundación Cardiovascular de Colombia. From resource individual information recollected from November 2015 to January 2018 of patients with stroke, we calculated event's costs considered:

1. Time hospitalization (general hospitalization, intensive care unit)
2. Medical supplies
3. Drug costs
4. Laboratory test
5. Cost of medical consultation
6. Cost of procedures (craniotomy, endoscopy, and colonoscopy).
7. Medical fees.

Drugs' costs were taken from the SISMED database, which is a ministry's of health database[14]. Drug's costs are reported in monthly Colombian pesos, for the use in the model the cost were convert in dollars using the representative rate for May of 2015. Cost of anticoagulation of warfarin and new oral anticoagulants were calculated from expert opinion of monthly controls of international normalized ratio (INR), and follow by specialist or general practitioner.

Sensitivity analyses

A several sensitivity analyses were conducted. As a first step a univariate analysis was useful for identify the most influence model's parameters and their impact on the final decision. Finally, a probabilistic sensitivity analysis was done, we used dirichlet distributions for probabilities and utilities, whereas normal distribution was used for cost (Table 1).

Table 1 Model parameters.

Parameters	Base	Ref	Distri	Parameters	Base	Ref	Distri
Stroke, Warfarin				pGIH_upper_mild_NOAC	0.48	(13)	
pStroke_war	0.0110	(12)	dirichlet	pGIH_upper_severe_NOAC	0.48	(13)	
pStroke_mild_warf	0.075	(13)		pGIH_upper_death_NOAC	0.05	(13)	
pStroke_mod_warf	0.41	(13)		pGIH_lower_mild_NOAC	0.44	(13)	
pStroke_sev_warf	0.465	(13)		**Other bleeding warfarin**			
Stroke, NOAC				pOtherbleeding_warf	0.0015	(13)	dirichlet
pstroke_apixaban	0.0088	(12)	dirichlet	pOtherbleeding_death_warf	0.003	(13)	dirichlet
pStroke_dabigatran	0.0091	(12)	dirichlet	**Other bleeding, NOAC**			
pStroke_rivaroxaban	0.0110	(12)	dirichlet	pOther_bleeding_NOAC	0.0015	(13)	dirichlet
pStroke_moderate_NOAC	0.415	(13)		pOther_bleeding_death_NOAC	0.003	(13)	dirichlet
pStroke_severe_NOAC	0.392	(13)		pGIH_lower_severe_NOAC	0.44	(13)	
pStroke_death_NOAC	0.102	(13)		pGIH_lower_death_NOAC	0.12	(13)	
ICH, warfarin				**COSTS**			
pICH_subdural_warf	0.54	(13)		warfarin	$12.5	(14)	normal
pICH_intracerebral_warf	0.46	(13)		Apixaban	$67.5	(14)	normal
pICH_subdural_mild_warf	0.4	(13)		Dabigatrán	$53.33	(14)	normal
pICH_subdural_severe_warf	0.4	(13)		Rivaroxaban	$45.16	(14)	normal
pICH_intracerebral_mild_warf	0.1	(13)		**Stable atrial fibrillation**			
pICH_intracerebral_severe_warf	0.35	(13)		cAFstable_warf	$20.91*		normal
pICH_intracerebral_death_warf	0.55	(13)		cStable_NOAC	$8*		normal
ICH, NOAC				**Event costs**, Stroke			
pICH_apixaban	0.0029	(12)	dirichlet	cStroke_mild	$1.000¶		normal
pICH_dabigatran	0.0031	(12)	dirichlet	cStroke_moderate	$2.869¶		normal
pICH_rivaroxaban	0.0039	(12)	dirichlet	cStroke_severe	$3.476¶		normal
pHIC_subdural_NOAC	0.54	(13)		**HIC, Cost**			
pHIC_intracerebral_NOAC	0.46	(13)		cICH_mild	$1.000¶		normal
pHIC_subdural_mild_NOAC	0.4	(13)		cICH_severe	$6.667¶		normal
pHIC_subdural_severe_NOAC	0.4	(13)		**GIH, Cost**			
pHIC_subdural_death_NOAC	0.2	(13)		cGIH_mild	$1.000¶		normal
pHIC_intracerebral_mild_NOAC	0.1	(13)		cGIH_moderate	$1.779¶		normal
pHIC_intracerebral_death_NOAC	0.55	(13)		cGIH_severe	$3.875¶		normal
GIH, warfarin				**Other costs**			
pGI_warf	0.0089	(12)	dirichlet	cOtherbleeding	$50¶		normal
pGI_upper_warf	0.76	(13)	dirichlet	cDeath	$3.000¶		normal
pGI_lower_warf	0.24	(13)		**EFFICACY**			
pGI_upper_mild_warf	0.48	(13)		eff_AF_estable	0.80	(12)	dirichlet
pGI_upper_severe_warf	0.48	(13)		eff_QALY_stroke_mild	0.51	(12)	dirichlet
pGI_upper_death_warf	0.04	(13)		eff_QALY_stroke_moderate	0.43	(12)	dirichlet
pGI_lower_mild_warf	0.44	(13)		eff_QALY_stroke_severe	0.35	(12)	dirichlet
pGI_lower_severe_warf	0.44	(13)		eff_QALY_HIC_mild	0.51	(12)	dirichlet
pGI_lower_death_warf	0.12	(13)		eff_QALY_HIC_severe	0.35	(12)	dirichlet
GIH, NOAC				eff_QALY_GIH_mild	0.75	(12)	dirichlet
pGIH_dabigatran	0.0154	(12)	dirichlet	eff_QALY_GIH_severe	0.50	(12)	dirichlet
pGIH_rivaroxaban	0.0156	(12)	dirichlet	eff_QALY_menorHemorhage	0.80	(12)	dirichlet
pGIH_apixaban	0.0058	(12)	dirichlet				
pGIH_upper_NOAC	0.76	(13)					
pGIH_lower_NOAC	0.24	(13)					

Distri: distribution; Ref: references; NOAC: New oral anticoagulants; *: expert opinion; ¶: costs from stroke cohort study.

Results

Base case analysis

The results were: a quality adjusted life expectancy of 1.48 years and total healthcare cost of $17 916 USD for apixaban, 1.49 QALY and cost of $18 122 USD for dabigatran, 1.32 QALY and cost of $21 966 USD for warfarin, and 1.24 QALY total cost of $24 547 USD for rivaroxaban (Table 2). The incremental cost and QALY for dabigatran compared to apixaban were $206 and 0.01, the incremental cost and QALY for warfarin compared to dabigatran were $3 844 USD and -0.17, and incremental cost and QALY of rivaroxaban compared with warfarin were $2 581 USD and -0.08. In the ranking (the less costly from the most costly) warfarin and Rivaroxaban were dominated (more expensive and less QALYs).

Table 2 Study's results.

		Base case			Probabilistic sensitivity analysis			
	Overall Cost	QALY	C/E	ICER	Overall Cost	QALY	C/E	ICER
Apixaban	$17 916	1.48	$12 116		$17 734	1.56	$11 357	
Dabigatrán	$18 122	1.49	$12 125	$12 998	$ 18 197	1.57	$11 564	$38 453
Warfarin	$21 966	1.32	$16 690	$-21 544	$20 477	1.40	$14 583	$-13 466
Rivaroxaban	$24 547	1.24	$19 750	$-25 536	$24 317	1.35	$17 996	$-12 156

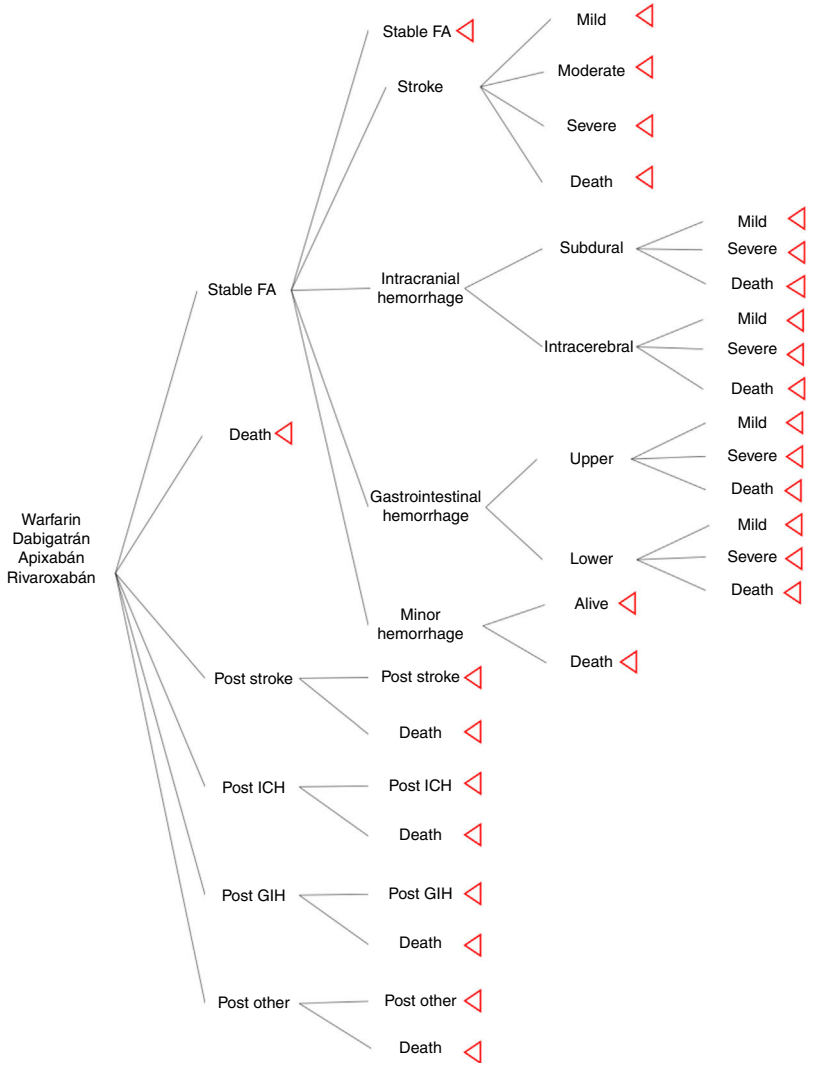


Figure 1 Model Inputs.

The ICER of apixaban compared to dabigatran (undominated alternatives) was $12 998 USD, and negatives ICER's for warfarin and rivaroxaban (dominated alternatives).

Deterministic sensitivity analysis

The tornado analysis (fig. 2) shows the most sensible variables of this model; probability of HIC and GIH (pHIC and pGIH) for apixaban and dabigatran were the most influential variables (fig. 1, appendix), stroke's probability for apixaban and dabigatran (pStroke) (fig. 2 appendix) also influenced in model. Apixaban and dabigatran's costs were the criteria that influenced the ICER in positive and negative way. Rest of variables were less influential.

Probabilistic sensitivity analysis

A series of analysis were made (Table 2), mean cost and QALYs were calculated based on probabilistic functions for the model parameters. Results are presented in Table 2, the

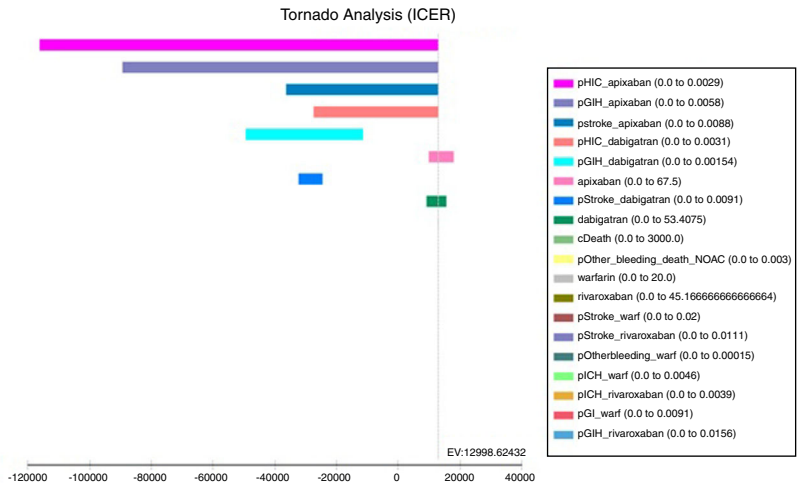


Figure 2 Analysis of ICER variations by parameter.

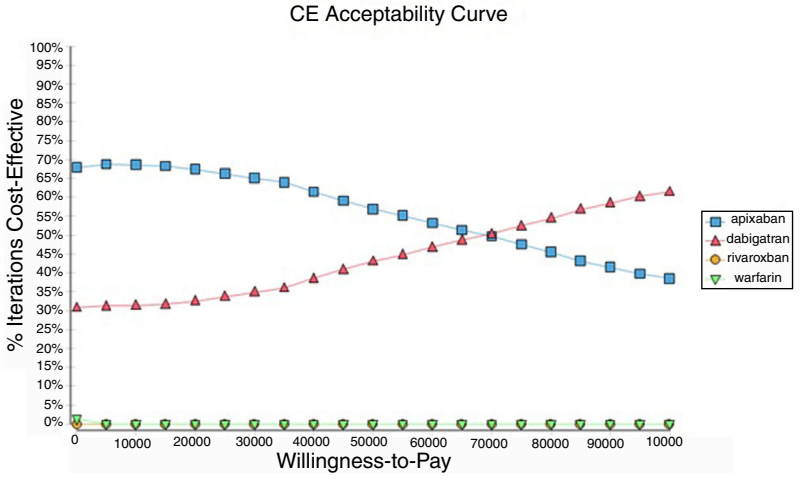


Figure 3 Analysis of cost-effectiveness probabilities.

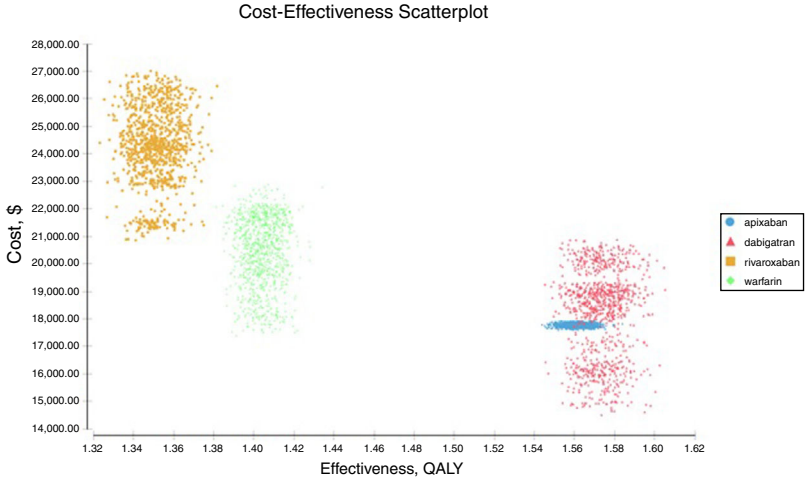


Figure 4 Monte Carlo Analysis, cost and QALY by iterations.

analysis was analysed under the WTP threshold of $9 000 USD. The median cost for apixaban was $17 734 USD with gained QALY of 1.56, Dabigatran median cost was $18 197 USD with gained QALY of 1.57, warfarin median cost was $20 477 USD with gained QALY 1.40, and rivaroxaban median cost of $24 317 USD gained QALY of 1.35. The ICER's for undominated alternatives was $38.453. At willingness to pay $9 000 USD, apixaban is cost-effective at 70% of iterations, dabigatran at 30% of iterations, warfarin and rivaroxaban were not (fig. 3). The cost-effectiveness scatterplot shows the point distribution of each option, apixaban's point distribution is close between them, and it confirms the result's robustness (fig. 4).

Discussion

We found that apixaban is the most cost-effective alternative for stroke prevention in atrial fibrillation from adverse event perspective, following by dabigatran 150, warfarin and finally rivaroxaban. This results from a less cost for apixaban and a minor difference of efficacy compared with dabigatran, and negative ICER's for warfarin and rivaroxaban indicates costlier and less efficacy alternatives. Apixaban accounted less overall cost due to smaller number of adverse events than dabigatran, warfarin and rivaroxaban, despite of greater drug's cost. The tornado type sensitivity analysis confirms that the most important model's parameters were those related to adverse events rates, this confirms the necessity of improve hemorrhage outcomes in anticoagulation models.

From this analysis warfarin was most cost-effective than rivaroxaban, driven by less overall cost (events, drug and controls costs) and best QALY's performance, the explanation is due to less gastrointestinal hemorrhage events in warfarin despite of more ICH; event rates has influence on both (cost and QALY). Clinical trials had shown an unexpected increase in gastrointestinal hemorrhage, especially among patients aged 75 years or over, a meta-analysis of 71.674 patients highlighted a 25% increase in gastrointestinal hemorrhage compared with warfarin[15]. This caused that warfarin had a best ICER than rivaroxaban (warfarin is dominant for rivaroxaban).

The ICERs can be used to set health priorities in three ways, (i) to minimize the expenditure to achieve a health effect target, (ii) to maximize the health benefits within budget and (iii) to consider cost-effective with an explicit threshold[16]. In Colombia, there is a lack of an explicit ICER to set efficiency treatments, due to the policy is focused on treatment access rather than principle of resources' maximization, but despite of it, WHO's recommendations about thresholds (less 1 GDP is highly C-E and 1-3 GDP is C-E) for middle income countries are considered[16]. From a new law called ''ley estatutaria de salud'' that ordered to ministry of health the adoption of a technical-scientific procedure to establish which services could be no afforded, the CEA could be used as a criterion by stakeholders. Is unknown which ICER would be used in the case to choose it, considering that opportunity cost is measure better with other threshold setting techniques as those that take into account the money invested [17]. Our ICER results are robust, uncertainty was measure, which allows the decision-making process —more transparent.

Study's strengths are: use of international validated anticoagulation model, the degree of complication was useful to ensure most of assumptions identified in clinical practice and hemorrhage localization, allowed the incorporation of adverse events by localization; we consider that it is a new model in oral anticoagulation, which incorporates more impact of adverse events. Model is robust, uncertainty for base case and other assumptions were measured, major changes in parameters must to be done to alter study's results. Other strength is the use of cost's information from a Cardiovascular Hospital and the bottom-up resources consumption calculation; this kind of resource utilization offer an opportunity for more detailed data collection[18]. Study's limitations are: use of international QALY's measurement (US), because of lack of Colombian's coefficients calculations for quantitative QALY assessment. We consider that efforts to measure coefficients in our population could be economic evaluations and patient's satisfaction studies more reliable than now, as well as national databases for costs that allow transparent decisions as those that law —indirectly claims.

Decision making process is quite complicated (by stakeholders' perspectives and interests), but decisions on which stakeholders opinions are considered, tend to increase the acceptance [19–21]. From this context, Health Technology Assessments (HTA) helps to provide input to decision making in policy and practice, its orientation is a decision making in a multidisciplinary, comprehensive nature and several perspectives; the main goal of such studies is to improve ''value for money'' in health care[22]. Multicriteria decision analysis (MCDA) is a tool to assist decision making process, which is used by national agencies to perform HTA as the Scottish Medicines Consortium (SMC). They stated criteria of clinical effectiveness and cost-effectiveness but allows other factors to play role[23], ICER is important but not —the only factor. New oral anticoagulants are used in clinical practice at this moment in Colombia, this from physician's consideration, but it is no widely used due to administrative restrictions that are changing from new administrative steps. New oral anticoagulants are afforded, but restrictions to contain the expenditure could be established, in this context new oral anticoagulants could be revaluated from other criteria than economic considerations; and a roadmap with stakeholder's participation must to be used.

Roads maps establish steps and the rules to be follow, it is crucial to reach transparent decision and moreover to improve the acceptance. The inclusion of new laws in Colombia lead us to speculate what would be the model to be adopted, but we consider that CEA remain plays a role in the decision process in Colombia; nevertheless, not as has been used until now to reject a technology as the only one criterion. Model parameters from real world data from Colombian' population have to be assess as those that allows QALY measuring and national costs. Major advances had done in Colombian' health system to ensure drug's access for continue giving the best technology as many as possible patients, more advances are necessary to do as defining of Colombian's road maps to decision making process. In this context, exists uncertainty about the play's role of new oral anticoagulants in clinical practice in our country.

Conclusions

Most of new oral anticoagulants are cost-effective for stroke prevention in oral anticoagulation in Colombia from adverse events perspectives, apixaban is the most cost-effective and rivaroxaban the last, none one is highly cost-effective if a 9 000 USD threshold is used, but are cost-effective. However warfarin remains be the status quo by proven efficacy and the known risk's profile. From changes in Colombian's health system is unknown the play's role of new oral anticoagulants in clinical practice.

Conflict of interest

None.

Acknowledgments

Net Cardiecol, COLCIENCIAS code: 5020-53-731809
Presentation at ISPOR-CO congress 2016, Bogota, Colombia.

References

1. Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. Am J Cardiol. 2012;110:453–60.
2. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ET. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. Gastroenterology. 2013;145:105–12.
3. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009:1139–51.
4. Granger CB, Hanna M, Wallentin L, et al. Apixaban versus warfarin in atrial fibrillation. N Eng J Med. 2012:366:88-90.
5. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Eng J Med. 2011;365:883–91.
6. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW, et al. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2015.
7. Tengs TO. Dying too soon: how cost-effectiveness analysis can save lives. National Center for Policy Analysis;. 1997.
8. Ferreira J, Mirco A. Systematic review of cost-effectiveness analyses of novel oral anticoagulants for stroke prevention in atrial fibrillation. Rev Port de Cardiol (English Edition). 2015;34:179–91.
9. Triana JJ, Castañeda C, Parada L, Otálora-Esteban M, Rosselli D. Costo-efectividad de dabigatrán comparado con warfarina para el tratamiento de pacientes con fibrilación auricular no valvular. Rev Colom Cardiol. 2016;23:82–6.
10. Peña AG. Costo-efectividad de los nuevos anticoagulantes orales en pacientes con fibrilacion auricular no valvular en Colombia. Value in Health. 2015;18:A829–30.
11. Pearce A, Haas M, Viney R. Are the true impacts of adverse events considered in economic models of antineoplastic drugs? a systematic review. Applied health economics and health policy. 2013;11:619–37.
12. Harrington AR, Armstrong EP, Nolan PE, Malone DC. Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. Stroke. 2013;44:1676–81.
13. Leigh P, White RH. An economic model of adverse events and costs for oral anticoagulants used for atrial fibrillation. Curr Med Reserch Op. 2007;23:2071–81.
14. Ministerio de salud y proteccion social. Sistema de información de precios de medicamentos. [Online] [Cited: 20 May 2015.] http://web.sispro.gov.co/WebPublico/SISMED/LibroVirtual/index2.html.
15. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. The Lancet. 2014;383:955–62.
16. Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost–effectiveness of interventions: alternative approaches. Bulletin of the World Health Organization. 2015;93:118–24.
17. Guidelines for the economic evaluation of healthcare technologies in Colombia: technical support documents. Centre for Health Economics, University of York, York, United Kingdom. s.l. : Instituto de evaluación tecnológica en Salud, 2014.
18. Mogyorosy Z, Smith P. The main methodological issues in costing health care services: a literature review (No. 007cherp);. 2005.
19. Sheppard SR. Participatory decision support for sustainable forest management: a framework for planning with local communities at the landscape level in Canada. Canadian J Forest Research. 2005:1515–26, iv.
20. Green AO, Hunton-Clarke L. A typology of stakeholder participation for company environmental decision-making. Business Strategy and the Environment, 2003;12(5):292-9.
21. Fritsch O, Newig J. Under Which Conditions Does Public Participation Really Advance Sustainability Goals? Findings of a Meta-Analysis of Stakeholder Involvement in Environmental Decision-making. 2007 Amsterdam Conf Hum Dimens Glob Environ Chang. 2007;May:24-26. http://www.2007amsterdamconference.org/Downloads/ AC2007_FritschNewig.pdf.
22. International Journal of Technology Assessment in Health Care, Health technology assessment. s.l. : 2009; 25.(S1).
23. Walker A. Challenges in Using MCDA for Reimbursement Decisions on New Medicines? Value in Health. 2016;19:123–4.