





Review of cost-effectiveness of antithrombotic alternatives in patients with atrial fibrillation

João Cruz Neto^{1*} , Liana de Oliveira Barros² ,
Sonia Samara Fonseca de Moraes² , Marcelo Gurgel Carlos da Silva² 

INTRODUCTION

A cerebrovascular accident is a pathological entity with the vascular impairment of sudden onset, which leads to the lowering of the level of consciousness, differentiating it into ischemic or hemorrhagic, with emphasis on cases related to atrial fibrillation (AF)^{1,2}.

Stroke is one of the main reasons for the use of public health resources, both in the inpatient and outpatient phases of the disease. Its expenses may be associated with the loss of early economic productivity, the development of psychological damage, the decrease in social interaction, and the loss of quality of life for the individual and their family^{3,4}.

It is estimated that Brazil has more than 2 million people over 18 years of age who have a stroke, with a higher prevalence in older adults⁵. Stroke is the second leading cause of death worldwide and the main cause of disability after a traumatic event. It is among the main problems in hospital urgencies and emergencies, representing 5.7 of a total of 58 million global deaths⁶.

It is estimated that the mean hospitalization cost per type of stroke in Brazilian services is US\$3,827 per year and increases to US\$9,505 in those patients with AF, while in countries such as the United States, it exceeds US\$40,743 if intravenous thrombolysis is associated^{7,8}.

The prevention of stroke and its complications by the administration of anticoagulants is one of the main objectives of the treatment for this public⁹. Most of the costs for stroke treatment are incurred in the first year after the injury, incurred by the highly complex procedures performed in this period⁷.

Currently, the therapeutic strategies available on a larger scale are vitamin K antagonists, such as warfarin, which reduce the risk of stroke complications by up to 64%⁹.

This study analyzes the evidence on the cost-effectiveness of antithrombotic alternatives in patients with AF as stroke prevention.

METHODS

This study comprises an integrative literature review. The research took place from August to September 2019 with the following steps:

1. The identification of the topic and selection of the research question using the Population (inpatients), Intervention (cost and cost analysis), Comparison (not applicable to the study), and Outcome (stroke, critical care, and AF) strategy. The research question was as follows: what is the scientific evidence on the cost-effectiveness of antithrombotic alternatives in patients with AF as stroke prevention?
2. The establishment of the inclusion and exclusion criteria: articles available electronically; originals; patients older than 18 years of age; studies published in Portuguese, English, or Spanish; and met the cost-effectiveness analysis method. There was no time limit. Those that did not address the investigated theme were excluded.
3. The establishment of a search strategy: Nursing Database (Base de dados em Enfermagem), Latin American and Caribbean Literature on Health Sciences database, Medical Literature Analysis and Retrieval System Online database, SCOPUS Preview, and Cumulative Index to Nursing and Allied Health Literature. In each database, the subject descriptors in the Medical Subject Heading of PubMed were delimited and crossed, and the following were used: Inpatients, Stroke, Critical Care,

¹Universidade Regional do Cariri, Departamento de Enfermagem – Crato (CE), Brazil.

²Universidade Estadual do Ceará, Programa de Pós Graduação em Saúde Coletiva – Fortaleza (CE), Brazil.

*Corresponding author: enfjncruz@gmail.com

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and Costs and cost analysis and their Descritores em Ciências da Saúde, with the Boolean operators AND and OR, in a paired manner by two different researchers. Titles were assessed, followed by abstracts and finally the full texts according to the exclusion and inclusion criteria established.

4. The presentation of the search and selection of data from the Preferred Reporting Items for Systematic Review and Meta-Analyses review protocol (Figure 1).
5. The evaluation and synthesis of studies: studies were evaluated according to the seven levels of evidence¹⁰. The data are presented in tables and narratives.

RESULTS

This review included 18 articles (Table 1)¹¹⁻²⁸ assessed according to authors, year of publication, study design, country of publication, therapeutic alternatives versus cost, and principal conclusions. In the cost analysis, the main currencies of circulation were the euro^{11-13,19-23} and the dollar^{14-18,20-22,24,25}.

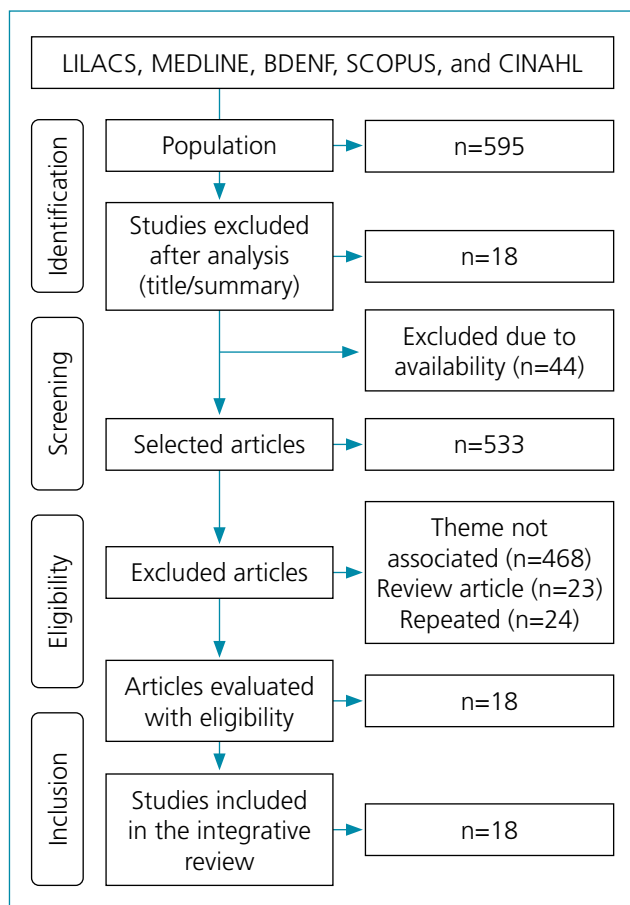


Figure 1. Flowchart of the article search and selection process, Brazil, in 2020.

The best quality-adjusted life years (QALYs) were conferred by the following: dabigatran, apixaban, warfarin, rivaroxaban, and edoxaban.

Apixaban effectively reduces the number of cardiovascular events in relation to the vitamin K analogs apixaban and warfarin. It may be the first-line treatment for stroke prevention in patients with AF¹¹ and is cost-effective¹⁷. Dabigatran was more cost-effective than rivaroxaban and warfarin for patients with AF, besides reducing the risk of stroke, pulmonary embolism, and intracranial hemorrhage with low bleeding^{12,14-20}.

DISCUSSION

It is known that AF is a cardiac abnormality characterized by the total disorganization of atrial electrical activity²⁹ and that stroke is one of the main complications³⁰. Therapy with oral anticoagulants plays a key role in the treatment of AF, avoiding the risk of thromboembolic stroke, although this therapy may bring some risk of intracerebral hemorrhage³¹.

The highest costs of stroke in healthcare systems are incurred by patients with AF, causing a burden of more than US\$1.5 million³² due to the multi-professional care required by these patients.

The economic impact caused by stroke is great, especially when associated with patients with AF³³, and therapeutic choices should be precise to minimize the associated costs. Thus, anticoagulant therapy is the most effective alternative for the prevention and treatment of thromboembolic diseases^{9,34}. Therefore, it is relevant to discuss the costs related to the effectiveness of the therapeutic options found in the market.

It was observed that the Markov model had more acceptances in the analyzed studies. This model is used for economic evaluations in healthcare systems, considering the evaluation of costs and clinical outcomes, especially in evaluating chronic diseases³⁵, which justifies its use in most of the studies included here.

Hospital services are overloaded with the demand from stroke centers, with an average of 10 patients/day⁹. This leads to the construction of research directed at pharmacological therapy with the best evidence of cost-effectiveness. A study on patients with ischemic and hemorrhagic stroke sequelae showed that the severity of symptoms was greater in those with AF, which is the group with significant expenses⁸.

Dabigatran is associated with significantly fewer hospitalizations in patients with AF than warfarin, and there was no significant difference in the mean cost of expenses between the two drugs³⁶. This corroborates the data obtained here regarding the decrease in total expenses by the addition of dabigatran therapy.

Dabigatran is also indicated with a decrease of US\$2,119,252,605 in 3 years in patients with nonvalvular

Table 1. Characterization of the articles included in the review regarding the research components, Brazil, in 2020.

Author/year/drawing/country/level of evidence	Alternative/monetary cost for better QALYs*	Main conclusions
Athanasakis et al. ¹¹ , 2017 Cost-effectiveness analysis with adapted Markov model/Cohort with 1,000 patients/Greece/IV	Apixaban/warfarin (€3,210.11) and VKA analogs (€2,019.29)	Apixaban is predictive in reducing the number of cardiovascular events compared with the vitamin K analogs apixaban and warfarin. Apixaban may be the first-line choice in stroke prevention treatment in patients with AF. It reduces mortality and morbidity and provides health system resolutions for populations with multiple comorbidities.
Shah et al. ¹² , 2016 Cost-effectiveness analysis with Markov model/Cohort with 10,000 patients/United States/IV	Dabigatran, rivaroxaban, apixaban, and edoxaban in the comparison between apixaban and warfarin (€25,816) and between ACO and warfarin (€100,000)	Oral anticoagulants (ACO) are the most effective alternative when the dose of warfarin is adjusted. Apixaban has high QALYs in AF patients. Dabigatran has higher QALYs for stroke risk. The QALYs of ACO have cost-effectiveness sensitive to the main drugs.
Esquivias et al. ¹³ , 2014 Cost-effectiveness analysis with the model adapted from Dorian/Cohort with 1,000 patients/Spain/IV	Apixaban (€30,000)	Apixaban is cost-effective in preventing stroke in patients with nonvalvular AF compared with acenocoumarol by 87%.
Peng et al. ¹⁴ , 2017 Markov model health cost-effectiveness panel/Cohort with 10,000 patients/United States/IV	Dabigatran/dabigatran (US\$3,343) rivaroxaban (US\$3,339)	Dabigatran is more cost-effective than rivaroxaban for patients with AF. Dabigatran further reduces the risk for stroke and pulmonary embolism with low bleeding and interdrug costs.
Lee et al. ¹⁵ , 2016 Cost-effectiveness analysis with Markov model/Cohort/China/IV	Apixaban (US\$53,315), rivaroxaban (US\$51,064), dabigatran 150 mg (US\$43,946), dabigatran 110 mg (US\$42,712), LAAO (US\$37,789), warfarin (US\$28,090), clopidogrel plus AAS (US\$26,287), AAS (US\$12,777)	LAAO is cost-effective compared with apixaban, rivaroxaban, dabigatran 150 mg, dabigatran 110 mg, warfarin, clopidogrel plus, and AAS in the prevention of stroke with nonvalvular AF.
Lee et al. ¹⁶ , 2012 Incremental cost-effectiveness with the Markov model/Randomized controlled trial/United States/II	Apixaban/apixaban (US\$44,232) and aspirin (US\$50,066).	Apixaban is more effective than aspirin; over time, it has become cost-effective and economically dominant.
Harrington et al. ¹⁷ , 2013 Cost-effectiveness analysis with Markov model/Cohort/United States/IV	Apixaban, dabigatran, rivaroxaban/compared warfarin with apixaban, apixaban (US\$7,513) was more cost effective.	Apixaban is cost-effective in treatment with thresholds >US\$40,000 per QALY. Warfarin is the most cost-effective AC in the treatment of patients with AF as prophylactic prevention of stroke.
Chang et al. ¹⁸ , 2013 Cost-effectiveness analysis/Cohort with 244 patients/China/IV	Dabigatran/dabigatran (US\$1,061) and warfarin (US\$1,306)	Dabigatran was cost-effective compared with warfarin, and the drug can be used for stroke prevention in patients with AF.
Wouters et al. ¹⁹ , 2013 Cost-effectiveness analysis with Markov model/Cohort with 10,000 patients/Belgium/IV	Dabigatran/dabigatran (€2,807) and warfarin (€20,000)	Dabigatran is the most cost-effective treatment for stroke prevention in patients with AF, representing good monetary value for healthcare settings.

Continue...

Table 1. Continuation.

Author/year/drawing/country/level of evidence	Alternative/monetary cost for better QALYs*	Main conclusions
Kansal et al. ²⁰ , 2012 Cost-effectiveness analysis with Markov model/Cohort with 100 patients/England/IV	Dabigatran and warfarin/ dabigatran (€10,424) and warfarin (€9,919)	Dabigatran treatment reduces the risk of stroke and intracranial hemorrhage compared with warfarin. Dabigatran is the cost-effective first-line alternative for patients with AF and decreases the risk of stroke.
Coyle et al. ²¹ , 2013 Cost-effectiveness analysis with the Markov model/Cohort/Canada/IV	Apixaban (€11,742), dabigatran (€50,000), warfarin and rivaroxaban	Rivaroxaban and dabigatran 110 mg are cost-effective, with dabigatran having less impact on bleeding.
Morais et al. ²² , 2014 Cost-effectiveness analysis with the Markov model/Nonrandomized study/Portugal/III	Rivaroxaban (€3,895), warfarin (€3,494)	Rivaroxaban showed greater cost-effectiveness than vitamin K analogs and is the indicated therapy for stroke prophylaxis in patients with AF.
Stevanovic et al. ²³ , 2014 Using efficacy by ARISTOTLE and AVERROES Markov Model/Cohort with 1,000 patients/Netherlands/IV	Apixaban (€14,113) and VKA (€14,904)	Apixaban is the most cost-effective alternative and has high treatment importance. However, due to the effects, it will be the second choice of treatment.
Reddy et al. ²⁴ , 2015 Cost-effectiveness analysis with the Markov model/Nonrandomized study/United States/III	Right atrial appendage closure (US\$20,892) and ACO (US\$20,924)	Appendix closure and OAC are cost-effective alternatives to stroke prevention in patients with AF
Ali et al. ²⁵ , 2012 Prospective observational study with 402 patients/United States/V	The cost of warfarin (US\$2,073) and dabigatran (US\$17,535)	Warfarin becomes more cost-effective for patients with AF in stroke prevention because dabigatran has the highest price.
Miguel et al. ²⁶ , 2013 Cost-effectiveness analysis with the Markov model/Nonrandomized study with 117 patients/Portugal/III	Dabigatran/dabigatran (€8,409)	Dabigatran reduces the risk of ischemic and hemorrhagic stroke and intracranial hemorrhage. It is shown to be cost-effective by waiving the international standardization rate.
Miguel and Ferreira ²⁷ , 2016 Cost-effectiveness analysis with the Markov model/Comparative study RE-LY and ROCKET AF with 71.693/Portugal/IV	Dabigatran and rivaroxaban/dabigatran (€11,858) and rivaroxaban (€12,223)	Dabigatran, in patients with AF, provides better clinical results than rivaroxaban in the same indication.
Magnuson et al. ²⁸ , 2015 Cost-effectiveness analysis with Markov model and ENGAGE AF-TIMI 48 with 21.105/Cohort study/United States/IV	Edoxaban and warfarin/ edoxaban (€43,370) and warfarin (€26,986)	Edoxaban becomes the most cost-effective alternative due to its wide sensitivity with impacts on post-stroke quality of life and bleeding.

QALY: quality-adjusted life-year; VKA: vitamin K antagonist; AF: atrial fibrillation; ACO: oral anticoagulant; LAAO: right atrial appendage transcatheter; AAS: acetylsalicylic acid; Monetary values were taxed according to the currency of each country at the time of the research.

AF in Colombia, being a viable alternative compared with apixaban, rivaroxaban, and warfarin in the medium term³⁷. In this study, the increase was more than US\$42,000, reinforcing that in years of gains, this therapeutic alternative exceeds the expectations of the payer, such as the public system, and improves the quality of life of the population that uses the drug.

Dabigatran and rivaroxaban have low medical costs for preventing stroke in people with AF³⁸. Other drugs are also noted for their cost-effectiveness. In this study, the new oral

anticoagulants (dabigatran, 110 mg; apixaban and rivaroxaban, 150 mg each) were found to be cost-effective compared with conventional strategies⁹.

CONCLUSIONS

Antithrombotic alternatives have been the target of international studies with the purpose of reducing public service costs and increasing patients' quality of life, considering alternatives

that are more effective in patients with different pathologies and those with direct impacts on public spending.

Apixaban and dabigatran were shown to be cost-effective regarding the quality years of life gained; both can be used in patients with AF, including the critically ill, to prevent hematological disorders and cardiovascular events such as stroke.

Studies in this area enable the first-line treatment in disease prevention and significantly reduce public spending, taking into account the years of life gained, reducing mortality and inhospital morbidity. Research on this topic

is also suggested in the Brazilian scenario to provide evidence for cost-effective alternatives with lower public service expenses.

AUTHORS' CONTRIBUTIONS

JCN: Conceptualization, Investigation, Writing – original draf. **LOB:** Data curation, Writing – original draf. **SSF:** Visualization, Writing – review & editing. **MGCS:** Supervision, Writing – review & editing.

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