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Latin American Clinical Epidemiology Network Series − Paper 2: Apixaban was cost-effective vs. acenocoumarol in patients with nonvalvular atrial fibrillation with moderate to severe risk of embolism in Chile

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Abstract

Objective: Nonvalvular atrial fibrillation (NVAF) is a risk factor for ischemic stroke and systemic embolism. New oral anticoagulants are currently available. The objective of this study was to assess the incremental cost−utility ratio (ICUR) for apixaban vs. acenocoumarol in patients treated in Chile's public health system.

Study Design and Setting: We assessed cost−utility from the payer perspective with a lifetime Markov model. Epidemiologic characteristics, costs, and utilities were obtained from a Chilean cohort; data were completed with information from international literature.

Results: Incremental costs when using apixaban vs. acenocoumarol over a lifetime are CH$2,108,600 with an incremental effectiveness of 0.173 years of life gained (YLG) and 0.182 quality-adjusted life-year (QALY). The ICUR of apixaban vs. acenocoumarol was CH$12,188,439 per YLG and CH$11,585,714 per QALY. One to 3 times gross domestic product (GDP) per capita threshold is acceptable based on World Health Organization (WHO) norms. Chilean GDP per capita was CH$7,797,021 in 2013. The sensitivity analysis shows that these results are sensitive to the ischemic stroke risk with apixaban, and the intracranial hemorrhage risk due to the use of acenocoumarol.

Conclusion: The use of apixaban in patients with NVAF in moderate-to-high risk of stroke is cost-effective, considering the payment threshold suggested by WHO.

Keywords: Atrial fibrillation; Cost−utility; Cost-effectiveness; Apixaban; Acenocoumarol; Novel anticoagulants

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia in adult patients. Its prevalence increases with advancing age, from 0.5% between the age of 40−50 up to 5−15% at the age of 80 [1,2]. Nonvalvular AF (NVAF) is associated with a three-to-five-fold increase in the risk of ischemic stroke (IS) and accounts for 1 of 4 to 1 of 6 of these IS episodes [3]. Although age-adjusted rates of stroke have declined in many high-income countries, they have risen in low- and middle-income countries (LMICs), making stroke prevention a priority for these countries [4].

Aspirin or oral anticoagulants are currently used for the prevention of brain and systemic embolism. Evidence on the use of aspirin is equivocal, so it is often reserved for patients with low risk of embolism [5]. The use of vitamin-K antagonists (VKAs) (warfarin or acenocoumarol) adjusted for an international normalized ratio (INR) between 2 and 3 aimed at the prevention of embolic events is supported

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Conflict of interest: The members of CIGES who participated in this study declare no other related conflicts of interest.

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LMIC challenges and opportunities

- Cardiovascular disease is a leading cause of death in low- and middle-income countries (LMICs), and lack of access to effective treatment is a major cause. For example, few patients with nonvalvular atrial fibrillation receive treatment to prevent stroke partly because of difficulties in monitoring prothrombin time.
- New oral anticoagulants are available for this condition, but these drugs, often more effective, safer, and more convenient to administer, are also more expensive.
- Such dilemmas are common in LMICs. Cost-effectiveness studies could resolve the problem, but limited information on national event rates and costs are a major challenge.
- Local retrospective cohort studies provide a fundamental tool to provide such information.

by multiple studies [5−7]. Nevertheless, the narrow treatment margin and the variability of plasma drug levels, both influenced by genetic factors, diet, drugs, and alcohol, demand for at least monthly controls with examinations to adjust the drug dose. When considering lifestyle changes and therapy-associated risks, both the number of patients suitable for therapy and treatment efficacy are limited [8].

Novel oral anticoagulants (NOACs) have shown similar or lower incidence of embolic and hemorrhagic complications compared to VKAs, with less drug-food interactions and no need for INR monitoring, resulting in simplified treatment [9−11]. Taking into account these advantages, clinical guidelines in developed countries now recommend NOACs as an alternative to warfarin [12]. However, in LMICs, these recommendations need to be balanced with considerations about the higher cost of NOACs.

Apixaban is a potent, selective, oral, direct factor Xa inhibitor. The ARISTOTLE study showed that apixaban is superior to warfarin in NVAF patients in the prevention of ischemic stroke or systemic embolism, with less bleeding and mortality [13]. Apixaban provides multiple benefits, but its price is notably higher than that of VKAs. In Chile, stroke is the leading cause of cardiovascular death [14]; therefore, an economic evaluation must be performed to quantify costs and benefits and guide both reimbursement decisions and clinical practice in terms of anticoagulant medication alternatives. The main objective of this study is to assess the incremental cost−utility ratio of apixaban vs. acenocoumarol in patients with a diagnosis of NVAF and risk of embolism. It was designed as a response to the local clinical practice needs. It was feasible because the Center for Clinical Epidemiology of the Universidad de la Frontera, part of the Latin American International Clinical Epidemiology (LATINCLEN) Network, brings together cardiologists that have participated in NOACs clinical trials and professionals trained in health economic and biostatisticians, all trained in the International Clinical Epidemiology Network (INCLEN) program. Economic evaluations have been of interest for Clinical Epidemiology since its beginning.

2. Methods

A cost−utility study was conducted to compare anticoagulation therapy with dose-adjusted acenocoumarol to an INR of 2−3 vs. apixaban 5 mg twice daily. The study population included Chilean adult patients with NVAF and $CHADS_2$ score ≥ 1, who were treated with acenocoumarol in the public health system. The study was conducted based on the payer perspective. A previously published and validated cost-effectiveness model was used for the purposes of this study [15]. Eleven permanent and three transient health states were included in the Markov model using 6-week cycles. Each transient state had a specific convalescence period, and its diagnostic and therapeutic cost was applied to each episode. A decreased utility was reported across the convalescence period, followed by normalization to patient's previous state. Similarly to other events, the risk can be increased in time and adjusted for time in therapeutic range (TTR) in this model.

Relations and possible transitions are depicted in Fig. 1. Age of onset in patients from the hypothetical cohort was 65 years, and the time horizon was life expectancy, with an annual discount rate of 3%, as recommended by Chilean authorities, applied both on costs and utilities from the first year. Results were expressed through incremental cost−utility ratio (ICUR), incremental cost per life-year (LY) gained, and per quality-adjusted life-year (QALY) gained. Sensitivity analyses using tornado plots were conducted on several variables of clinical interest considering event incidence, costs, and utilities. Probabilistic sensitivity analysis was performed by running 2,000 simulations.

2.1. Ischemic stroke

The risk of ischemic stroke is based on age, $CHADS_2$ score, and quality of anticoagulation. The model allowed for the analysis of the impact of these variables and leads to increased baseline risk for each life decade in the age variable. Risk is added based on $CHADS_2$ score at the beginning of the program and adjusted for increasing in stroke risk on 10-year basis, but $CHADS_2$ value through time remained unmodified. Anticoagulation quality was measured at baseline through the TTR variable, representing the time patients had an INR within 2−3 while on treatment [16]. These center-based TTRs were assumed constant throughout the model life cycle. A modified Rankin scale was used to assess the severity [17] of ischemic