Cost-Utility Analysis of Oral Anticoagulants for Nonvalvular Atrial Fibrillation Patients at the Police General Hospital, Bangkok, Thailand

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ABSTRACT

Purpose: The genetic polymorphism was one of the major considerations for adjusting doses of warfarin in Thai individuals. As a result, new oral anticoagulants (NOACs) were introduced to achieve therapeutic goals in stroke prevention in atrial fibrillation (SPAF) patients. However, a cost-utility analysis in a population-specific model was lacking in Thailand. This study was performed to determine which NOACs yielded population-specific, cost-effective results for SPAF compared with warfarin from both governmental and societal perspectives in Thailand.

Methods: A simplified Markov health state model was constructed to calculate the lifetime cost, life-years saved, and quality-adjusted life-years (QALYs) gained. Asia-specific clinical event parameters were defined from systematic searches of PubMed. Cost and utility input was obtained from hospital based data collection.

Findings: Although NOACs produced more life-years saved and QALYs gained resulting from the base-case versus warfarin, the lifetime costs of new alternatives increased to >1.4 times the comparative cost of warfarin. This caused an incremental cost-effective ratio that exceeded Thailand's cost-effectiveness threshold. The probabilistic sensitivity analysis denoted the robustness of our model and revealed that dose-adjusted warfarin was the most cost-effective option in >99% of iterations. NOACs produced cost-effective results when the medication unit cost was decreased by at least 85%.

Implications: According to the results of this first cost-utility analysis in Thailand, warfarin is still the most cost-effective medication for SPAF from any perspective in Thailand at the threshold recommended by our health technology assessment guidelines. (*Clin Ther.* 2014;36:1389–1394) © 2014 Elsevier HS Journals, Inc. All rights reserved.

Key words: Asian, atrial fibrillation, cost utility, new oral anticoagulant, stroke.

INTRODUCTION

Ischemic stroke is the most common thromboembolic complication found in NVAF patients.[1] Although the prevalence of nonvalvular atrial fibrillation (NVAF) in Asia is less than half that in the West,[2] the risk of thromboembolic events is 2 times higher.[3] In particular, neurologic deficits resulting from stroke events leading to family dependence and financial burden represent the most concerning issue. Consequently, the Heart Association of Thailand has issued recommendations on the use of anticoagulants to prevent stroke in moderate- to high-risk patients.[2]

Even though warfarin, the standard anticoagulant preferred in Thailand, has many advantages (eg, familiar to most physicians, comparatively inexpensive, ability to predict the therapeutic efficacy and safety from the international normalized ratio (INR), availability of the exact antidote),[2] the core limitations of its use are interindividual variation including genetic polymorphism, slow onset and offset of action, numerous drug and food interactions, and inconvenience of frequent INR monitoring.[4] As a result, new oral anticoagulants (NOACs) were developed to overcome these limitations.[5]

In Thailand, there are currently 3 NOACs available for stroke prevention in atrial fibrillation (SPAF) that have been approved by the US Food and Drug Administration: 1 is a direct thrombin inhibitor (dabigatran) and 2 are direct factor Xa inhibitors

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(rivaroxaban and apixaban). Their primary advantages over warfarin are that their thromboembolic preventive effects are at least equal to those of warfarin but with no INR monitoring required.[5] Conversely, the budget gain from medical expenses was often realized as a financial burden in Thailand. Finally, there were no population-specific cost-effectiveness studies available, either in Thailand specifically or in Asia in general.

Therefore, this study was conducted to evaluate the cost-utility analysis of NOACs compared with warfarin for SPAF in the Thailand using the Asia-Pacific subgroup analysis parameters from 3 main studies which had been submitted to the US Food and Drug Administration for approval: the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy),[6] ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation),[7] and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation).[8]

METHODS

Model Structure

A Markov health state model was adapted from related health technology assessment literature[9,10] and reviewed by a cardiologist (Supplemental Figure 1). The model cohorts were patients older than 65 years of age with newly diagnosed NVAF, a moderate to high risk of stroke ($CHADS_2$ score [Congestive heart failure, Hypertension, Age $\geq$75, Diabetes mellitus, and prior Stroke or transient ischemic attack (doubled)] $\geq$2), and no history of stroke. Each patient included in the model was assigned to one of the following strategies: dose-adjusted warfarin (target INR of 2–3), dabigatran 150 mg BID, dabigatran 110 mg BID, rivaroxaban 20 mg/day OD, or apixaban 5 mg BID. Starting from a well state, each selected patient could then be in any one of 10 states of health in 1-year cycles for 30 years or until death. The 10 health states included in the model were as follows: well/full recovery from any health state; ischemic stroke with/without complications (eg, pneumonia, seizure, urinary tract infection, pressure sore); nondisabling ischemic stroke (defined by modified Rankin Scale [mRS] scores of 0–1); disabling ischemic stroke (defined by mRS scores of 2–5); major bleeding (defined by intracranial hemorrhage) with/without complications (eg, hydrocephalus, seizures, venous thrombotic events, hyperglycemia, increased blood pressure, fever, infections), extracranial hemorrhage (eg, major gastrointestinal bleeding with/without complications such as hypovolemia and shock); nondisabling major bleeding (defined by mRS scores of 0–2); disabling major bleeding (defined by mRS scores of 3–5); myocardial infarction with/without complications (eg, acute heart failure, arrhythmia); full recovery from myocardial infarction (defined as a successful percutaneous coronary intervention); and death (from any health state including natural cause of death). The assumptions were set into the model as (1) the treatment effect exhibited immediately after starting and remaining constant throughout life, (2) the adherence to each alternative was similar, and (3) drug was discontinued until the patient died.

Clinical Treatment Effect and Transitional Probability Parameters

A systematic review was conducted in MEDLINE via PubMed to gather clinical model input. Three notable published studies (subgroup analysis of RE-LY, ROCKET-AF, and ARISTOTLE) were recruited and their relevant data extracted to obtain the relative risk of such alternatives (Supplemental Table I). The baseline annual rate of important clinical events while taking warfarin were calculated by the pooled mean and SD from Asia-Pacific regional data according to the formula reported elsewhere.[11] The pooled estimation of clinical relevance events of NOACs was derived from a meta-analysis using Review Manager software version 5.2. The mortality rate was multiplied by factors of 3.7, 3.7, and 1.05 after ischemic stroke, intracranial hemorrhage, and myocardial infarction, respectively.[9] The transitional probabilities of health outcomes were obtained from local literature (Thailand journal) to reflect our context (Supplemental Table I).

Because Asian individuals are more prone to experiencing dyspepsia than white individuals,[3] that was the only adverse drug reaction (ADR) in this model. The ADR event rate of NOACs other than dabigatran was assumed to be equal to that of warfarin. Minor bleeding rates and consequences were excluded from our analysis because most of our patients were advised in self-management by a team of clinical pharmacists so fewer patients presented to a hospital for further investigation or treatment in such cases.

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