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Cost-Effectiveness of the Combined Use of Warfarin and Low-Dose Aspirin versus Warfarin Alone in Egyptian Patients with Aortic Valve Replacements: A Markov Model

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ABSTRACT

Background: The combination of antiplatelet and anticoagulant therapy significantly reduces the rate of thromboembolic events in patients with heart valves compared with anticoagulant therapy alone. Cost-effectiveness of this therapy in Egypt, however, has not yet been established. **Objective:** The aim of the present study was to evaluate the cost-effectiveness of the combined use of warfarin and low-dose aspirin (100 mg) versus warfarin alone in patients with mechanical aortic heart valve prostheses who began therapy at the age of 50 to 60 years over a 5-year period from the perspective of the medical providers. **Methods:** A cohort Markov process model with five health states (recovery, reoperation, bleeding, thromboembolism, and death) based on Egyptian clinical practice was derived from published sources. The clinical parameters were derived from meta-analyses of randomized controlled trials of patients with mechanical valve prostheses. The quality of life of the health states was derived using the available published data. Direct medical costs were obtained from four top-rated governmental cardiology hospitals in Egypt. All costs and effects were discounted at 3.5% annually. All costs were converted using the purchasing power parity rate and are reported in US $ for the financial year of 2013. **Results:** The total quality-adjusted life-years (QALYs) were estimated to be 1.1616 and 1.1199 for the warfarin plus aspirin group and the warfarin group, respectively, which resulted in a difference of 0.0416 QALYs. The total costs for the warfarin plus aspirin group and the warfarin group were US $307.33 and US $315.25, respectively (the difference was US $7.92), which yielded an incremental cost-effectiveness ratio of −190.38 for the warfarin plus aspirin group. Thus, the combined therapy was dominant. Various one-way sensitivity analyses indicated that probabilities of reoperation and bleeding in the recovery state had the greatest effects on incremental costs. The model parameters that had the greatest effects on incremental QALYs were the relative risk reduction of death and the utility value in the recovery state. **Conclusions:** The present study is the first cost-utility analysis to conclude that, from the perspective of Egyptian medical providers, combined therapy is more effective and less costly than warfarin alone for patients with mechanical aortic valve prostheses. For clinicians and patients who choose to focus on minimizing thromboembolic risk, these results suggest that combined therapy offers the best protection. This study helps to inform decisions about the allocation of health care system resources and to achieve better health in the Egyptian population.

Keywords: aortic valve replacement, aspirin, cost-effectiveness, Egypt, warfarin.

Introduction

In developing countries, one of the major causes of valvular heart disease that requires valve replacement is rheumatic fever affecting young adults [1]. In Africa, the combination of a lack of resources, a lack of infrastructure, political, social, and economic instability, poverty, overcrowding, and malnutrition contributes to the persistence of the high burden of rheumatic valvular heart, which later requires surgery [2]. Although mechanical prostheses have excellent durabilities, they require lifelong anticoagulation therapy to minimize risks of thrombosis and embolism. Warfarin therapy reduces disability and fatal thromboembolic events, but it can also cause disabling and fatal hemorrhagic events. Anticoagulants without antiplatelet agents do not provide adequate protection for patients with mechanical aortic heart valve prostheses [3,4]. The addition of aspirin (80–160 mg

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daily) to warfarin therapy may reduce the risk of thromboembolism and valve thrombosis [5,6].

The initiation of an effective early antithrombotic therapy is important because of its potential effect on the rate of early thromboembolic complications after mechanical aortic heart valve implantation [7,8]. An important question that remains to be answered is whether the combined use of warfarin and low-dose aspirin is more cost-effective than warfarin alone in Egyptian governmental hospitals from the perspective of medical providers. This question is particularly important because a misconception exists in the Egyptian medical community that the added clinical benefit of reducing the risk of complications is not worth the cost. Decision analysis is a quantitative method for synthesizing data from numerous sources for the evaluation of treatment alternatives and was developed to determine the cost-effectiveness of the combined use of warfarin and low-dose aspirin as compared with warfarin only.

Objective

The objective of this study was to evaluate, from the perspective of the medical provider, over a 5-year period, the cost-effectiveness of the combined use of warfarin and 100-mg aspirin compared with that of warfarin alone in patients with mechanical aortic heart valve prostheses who began therapy between the ages of 50 and 60 years.

Methods

A half-cycle corrected Markov cohort process model with the five mutually exclusive health states (recovery, reoperation, bleeding, thromboembolism, and death) was developed (Fig. 1). The structure of this model reflects the natural history of the disease, the current treatment practices, and the published studies in this disease area [9]. This type of decision model is used for analyzing clinical problems involving risks that change or occur repeatedly over time [10]. The five identified health states of the model structure correspond to the real practice of patient management in Egypt and remain as simple as possible. The health states (i.e., model contents) were validated by clinical experts and the data that were available from the authors' institutions. The model was built to reflect patients who began therapy between the ages of 50 and 60 years. Although aortic valve replacement (AVR) can be done at any age, it is most commonly done in patients 45 years and older. A time horizon of 5 years was selected to reflect the long-term consequences of the decisions. To simplify the model, it was adapted to exclude clinical events that were not expected to differ across the compared patients [11] (e.g., perioperative mortality due to primary AVR and prosthetic valve endocarditis); however, the valve-related excess mortality rate described below was included. The combined use of adjusted-dose warfarin and 100-mg oral aspirin (international normalized ratio 2–3) was compared with the use of adjusted-dose warfarin (international normalized ratio 2–3) alone, which is the currently recommended practice. The transition probabilities from the recovery health state to the reoperation, bleeding, thromboembolism, and death states were derived from previously published sources [9,12].

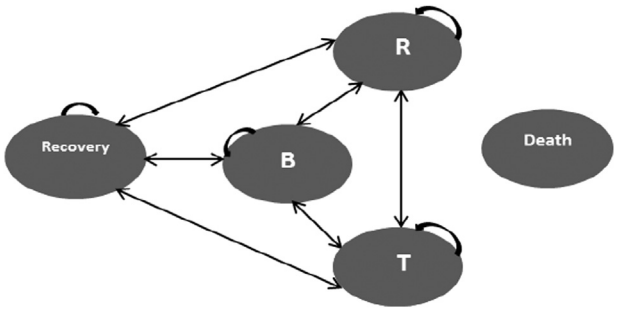

Fig. 1 – Markov state-transition diagram. Not shown are the transitions to the death state. B, bleeding; R, reoperation; T, thromboembolism.

A comprehensive search of PubMed and MEDLINE was conducted for English articles published between 1985 and June 2013 to retrieve the available published data regarding the probabilities of the health states, the relative risks of the combination therapy, and the quality of life in the health states. Randomized controlled trials (RCTs), systematic reviews, and meta-analyses of RCTs were chosen because they provide the least biased and most robust evidence regarding treatment. When RCTs were not available, observational studies were included after considering expert opinions regarding the synthesis of the clinical evidence. Articles that addressed the long-term management of patients with prosthetic heart valves were selected on the basis of terms related to the clinical conditions and the cost-effectiveness of the combination; these terms included the following: "cost-effectiveness," "aortic valve replacement," "antithrombotic," "antiplatelet," "anticoagulation," "aspirin," "vitamin K antagonist," "warfarin," "thrombosis," "bleeding," "randomized controlled trial," "randomized," "controlled trial," "meta-analysis," and "systematic review." Articles that exclusively included trials that focused on elderly patients were excluded because these trials evaluated a different patient population. Twenty-two relevant articles were identified by this electronic search and were reviewed, and six articles were excluded for the above-mentioned reasons.

The cycle length of the model was 1 month to allow for a precise estimation of the timing of events and related costs because patients are unlikely to experience more than one major event during this time [13]. This study adopted the perspective of a medical provider seeking to maximize the health gains of the population while representing the most efficient use of the finite resources available to Egyptian governmental hospitals [11]. All costs and effects were discounted at 3.5% annually as recommended by Egyptian guidelines [11].

Clinical Parameters

The following five health states were studied: the recovery state, which was defined by the patients being alive without event or recovering after an event; reoperation, which was defined by patients undergoing reoperation or suffering operative morbidity; bleeding, which was defined by the requirement of hospitalization or blood transfusion for a major bleeding event; thromboembolism, which was defined by the patients suffering a thromboembolic event with morbidity; and death, which was defined as death from any cause. All patients who underwent the indexed surgery without morbidity were initially defined as being in the recovery state. Thus, with every cycle, the patients who survived the index surgery could remain in their current health state or could experience the following: bleeding (fatal or nonfatal), valve thrombosis followed by reoperation (fatal or nonfatal), thromboembolism, or death from any cause.

Several assumptions were incorporated to simplify the model. First, the population was assumed to be free of noncardiac life-threatening morbidities. There were neither explicit indications nor contraindications for anticoagulation. Second, we assumed that patients with AVR who experienced major bleeding continued to receive oral anticoagulant therapy because studies have shown that the risks of thromboembolism in patients with mechanical valves who are not on anticoagulant therapy exceed the risks of recurrent bleeding in those receiving anticoagulation