VALUE IN HEALTH ▮ (2017) ▮▮▮–▮▮▮

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Comparison of Oral Anticoagulants for Stroke Prevention in Nonvalvular Atrial Fibrillation: A Multicriteria Decision Analysis

Tommi Tervonen, PhD[1,], Anastasia Ustyugova, MD, PhD[2], Sumitra Sri Bhashyam, PhD[1], Gregory Y.H. Lip, MD[3,4], Paolo Verdecchia, MD, PhD[5], Ryan Kwan, MA[6], Savion Gropper, MD, PhD[7], Jutta Heinrich-Nols, MD[7], Kevin Marsh, PhD[1]*

[1]*Evidera, London, UK;* [2]*Boehringer Ingelheim GmbH, Ingelheim, Germany;* [3]*Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK;* [4]*Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark;* [5]*Hospital of Assisi, Assisi, Italy;* [6]*Boehringer Ingelheim (Canada) Ltd., Burlington, Ontario, Canada;* [7]*Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany*

ABSTRACT

Background: Decision on the most appropriate oral anticoagulation therapy for stroke prevention in patients with nonvalvular atrial fibrillation is difficult because multiple treatment options are available, and these vary in their clinical effects and relevant nonclinical characteristics. **Objectives:** To use a multicriteria decision analysis (MCDA) to compare the oral anticoagulants apixaban, dabigatran, edoxaban, rivaroxaban, and vitamin K antagonist (VKAs; specifically warfarin) in patients with nonvalvular atrial fibrillation. **Methods:** We identified the evaluation criteria through a targeted literature review and clinical judgment. The final evaluation model included nine clinical events and four other criteria. We ranked possibly fatal clinical event criteria on the basis of the differences in risks of fatal events and the corresponding window of therapeutic opportunity, as observed in clinical trials. Clinical judgment was used to rank other criteria. Full criteria ranking was used to calculate centroid weights, which were combined with individual treatment performances to estimate the overall value score for each treatment. **Results:** Using such an MCDA, dabigatran yielded the highest overall value, approximately 6% higher than that of the second-best treatment, apixaban. Dabigatran also had the highest first-rank probability (0.72) in the probabilistic sensitivity analysis. Rivaroxaban performed worse than the other non-VKA oral anticoagulants, but better than VKAs (with both having 0.00 first-rank probability). The results were insensitive to changes in model structure. **Conclusions:** When all key oral anticoagulant value criteria and their relative importance are investigated in an MCDA, dabigatran appears to rank the highest and warfarin the lowest.

Keywords: anticoagulation, atrial fibrillation, decision analysis, multicriteria decision analysis.

Introduction

Oral anticoagulants (OACs) are widely prescribed for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF). This class of drugs includes vitamin K antagonists (VKAs; e.g., warfarin) and novel oral anticoagulants (NOACs; apixaban, dabigatran, edoxaban, and rivaroxaban). Cost-effectiveness of OACs is well understood [1–3] and the cost/quality-adjusted life-year framework allows an assessment of OACs from a strictly pharmacoeconomical point of view. Nevertheless, OACs vary considerably in their nonclinical characteristics, such as frequency of administration [4] and reversibility of their effect, that are not captured in traditional pharmacoeconomical analyses.

Multicriteria decision analysis (MCDA) is a technique that can both capture the performance of treatments across such multiple dimensions [5] and aggregate these dimensions into an overall quantitative estimate of treatment value by taking into account the estimates of their relative importance (weight) [6]. The ability of MCDA to support treatment evaluation has led to its increased use in health care circles [7], with recent reviews indicating MCDA to be a particularly appropriate methodology for drug benefit-risk assessment [8,9]. For instance, the benefit-risk methodology

Conflicts of interest: T. Tervonen, S. Sri Bhashyam, and K. Marsh are employees of Evidera, a consultancy that advises all major pharmaceutical manufacturers. A. Ustyugova, R. Kwan, S. Gropper, and J. Heinrich-Nols are employees of Boehringer Ingelheim. G. Y. H. Lip has provided consultant services for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo and has received speaker honoraria from Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. P. Verdecchia has received speaker honoraria from Boehringer Ingelheim, Bayer, BMS-Pfizer, and Daiichi-Sankyo and has consulted for Boehringer Ingelheim.

* *Address correspondence to:* Tommi Tervonen, Evidera, Metro Building, 6th Floor, 1 Butterwick, London W6 8DL, UK.
E-mail: tommi.tervonen@evidera.com.

1098-3015$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2017.06.006

project of the European Medicines Agency stated MCDA to be "the most relevant tool" for benefit-risk assessment [10]. Furthermore, guidance for using MCDA in assessing treatments is available from a dedicated task force of the International Society for Pharmacoeconomics and Outcomes Research [11,12]. MCDA has been used successfully to compare and rank cardiovascular drugs within classes such as statins [5,13,14], antiplatelet drugs, and anticoagulants [15–17]. Nevertheless, previous MCDA studies of OACs evaluated only a limited set of criteria of treatment performance [16], included only a subset of available treatments [15,17], and/or double-counted mortality rates [17].

This article reports an MCDA designed to generate a comprehensive measure of the benefit of OACs for stroke prevention in patients with NVAF. We took the perspective of assessing the value of OACs for a population of patients, making the results useful for informing both formulary decisions and prescription decisions. We compared five OACs (apixaban 5/2.5 mg bid, dabigatran 150/110 mg bid, edoxaban 60/30 mg qd, rivaroxaban 20/15 mg qd, and warfarin qd) according to their dosing recommendations for stroke prevention in patients with NVAF in the European Union. Also, although acknowledging that various VKAs can be prescribed in NVAF, we explicitly labeled the VKA in our study as warfarin because this is by far the most commonly used drug of this type, a traditional standard of care, and the reference treatment in most comparative studies of anticoagulants.

The contribution of this article is twofold. First, the reported MCDA is the first comparing all available OACs on a range of criteria that fulfill the MCDA requirements [5,6], including other than clinical event attributes that may influence treatment choice. Second, a novel rank-based weighting methodology is adopted, in which the criteria are prioritized mainly on the basis of their impact on a patient undergoing the treatment.

Methods

In line with recent guidance on conducting MCDA studies in comparative treatment assessment [5,12], the construction of an MCDA evaluation model for this analysis involved the following five steps:

1. Definition of the various criteria on which treatment performance was to be evaluated (the "evaluation criteria");
2. Measuring the performance of treatments on these criteria;
3. Rating the value of different levels of performance for each criterion (i.e., forming "criteria scales");
4. Definition of weights to reflect the relative importance of each criterion;
5. Aggregation of data on performance with the weights to derive an overall measure of value and analysis of uncertainty associated with the model's results.

Definition of the Evaluation Criteria

An initial list of evaluation criteria relevant for OAC choice was identified using five published articles on the treatment value of OACs [15–19] and authors' expert opinion. The final list (presented in Table 1) was developed to meet the MCDA criteria requirements [5,6], which state that the criteria need to be value-relevant, clear, measurable, complete, and nonredundant. For example, cardiovascular mortality was excluded because of redundancy with fatal clinical events, and all-cause mortality was excluded because it was believed that any differences in rates of fatal noncardiovascular events are not attributable to the anticoagulation effect of OACs. Details on the justification for the inclusion and exclusion of particular criteria are included in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2017.06.006.

Measurement of Treatment Performances

To derive treatment performance measurements for the clinical event criteria, the MCDA relied on the pivotal trials of NOACs (namely, Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) [20], Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) [21], Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction Study 48 (ENGAGE AF-TIMI 48) [22], and Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with VItamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) [23]) as primary data sources. Clinical event hazard ratios of NOACs versus warfarin were extracted from ARISTOTLE [21], ENGAGE (high-dose group, in which 74.6% received 60 mg qd and 25.4% received 30 mg qd) [22], and ROCKET-AF (safety, as-treated population) [23] publications and from RE-LY statistical analyses. Pivotal trial publications for apixaban, edoxaban, and rivaroxaban describe results for the trial population, among which some patients received the lower recommended dose adjusted on the basis of prespecified characteristics. The population for dabigatran was defined in the post hoc analysis, using the full RE-LY trial cohort, according to dosing recommendations for stroke prevention in patients with NVAF in the European Union, corresponding to 84% receiving 150 mg bid and the rest receiving 110 mg bid [24].

To account for possible variation in population baseline risk between the trials, a common baseline risk was used across treatments: the warfarin arm of the RE-LY trial [20]. Hazard ratio estimates for events with NOACs compared with warfarin were multiplied with warfarin event risk estimates to generate absolute risk estimates for the NOACs [25]. For some criteria, data were not available for all the treatments under consideration, and additional assumptions were therefore required to generate performance estimates. Data sources and assumptions are presented in Table 1. The transformation required to obtain absolute risk measurements resulted in performance estimates that were not parametrically distributed, and so treatment performances were instead estimated using a sampling technique. Specifically, 10,000 samples were drawn for each clinical event criterion, and any required transformations were performed for the individual draws. Table 2 presents the estimated absolute risks for each treatment on all clinical event criteria.

In addition to the clinical event criteria, the treatments were evaluated against the following other criteria: administration frequency, interactions with food, availability of real-world evidence (RWE) of effectiveness and safety, and availability of treatment-reversal agent. The administration frequency was obtained from product labels and consisted of two values: once daily ("best") and twice daily ("worst"). We limited food interaction considerations to strict dietary restrictions that were relevant only to warfarin. A simple binary scale for RWE aimed to evaluate whether the RWE available for a treatment supported the clinical benefits and safety profile established in pivotal trials ("best") or whether such evidence was not available ("worst"). All OACs apart from edoxaban have RWE studies published in the scientific literature and were thus considered to have good quality RWE available. Treatment performances for these criteria are presented in Table 2.

Development of the Criteria Scales

Weights in additive-value models, such as the one used in this MCDA, represent trade-off ratios over a defined scale for each