Cost-effectiveness Analysis for Apixaban in the Acute Treatment and Prevention of Venous Thromboembolism in the Netherlands

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ABSTRACT

Purpose: Low-molecular weight heparin (LMWH) followed by vitamin K antagonists (VKAs) are the current standard treatment of acute venous thromboembolism (VTE) and prevention of recurrent VTE. The direct oral anticoagulant apixaban was recently found noninferior in efficacy and superior in preventing major bleeding compared with LMWH/VKAs in the AMPLIFY (Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy) trial. The objective of this study was to calculate the cost-effectiveness of apixaban compared with LMWH/VKA in the treatment of acute VTE and prevention of recurrent VTE in the Netherlands.

Methods: A Markov model was designed to simulate a cohort of 1,000 VTE patients receiving either apixaban or LMWH/VKA. Transition probabilities, costs, and utilities were obtained from the AMPLIFY trial and other literature. The incremental cost-effectiveness ratio (ICER) was calculated from the societal perspective; therefore, the model included both direct (inside and outside the health care sector) and indirect costs. In the univariate and probabilistic sensitivity analyses (PSAs) the robustness of the results was tested, and various additional scenario analyses were conducted.

Findings: In the base-case analysis, apixaban saved €236 and 0.044 quality-adjusted life years (QALYs) and 0.039 LYs were gained compared with LMWH/VKA. In the univariate sensitivity analysis the model appeared to be robust. The results of 2,000 iterations in the PSA found that the probability of apixaban being cost-effective at a willingness-to-pay threshold of €20,000/QALY was 100% and cost-saving was 94%. The scenario of 18-month treatment duration was the only scenario not indicating cost-savings with an ICER of €425/QALY.

Implications: In acute anticoagulation use apixaban was found to be cost-saving. A longer anticoagulation period (18 months) resulted in a higher difference in drug costs, indicating a higher ICER. The cost-effectiveness of long-term or life-long use should be examined in future research. (*Clin Ther.* 2017;39:288–302) © 2017 Elsevier HS Journals, Inc. All rights reserved.

Key words: apixaban, cost-effectiveness, direct oral anticoagulant, venous thromboembolism.

INTRODUCTION

Deep vein thromboembolism (DVT) and pulmonary embolism (PE) are collectively known as venous thromboembolism (VTE). DVT is a blood thrombus mostly seen in the calf veins, and PE is the result of a free clot causing obstruction in the pulmonary veins. Diagnosis of VTE is based on the symptoms and a D-dimer test, and risk factors (eg, recent surgery, smoking) can confirm the suspicion.[1]

In 2014 a total of approximately 60,000 VTE patients, including nearly 19,000 new patients, were monitored by the Dutch Thrombotic Service.[2] Of these patients 56% were treated for (recurrent) DVT and 44% for (recurrent) PE.[2] In general practice, the incidence of DVT and PE is respectively 0.5 to 1.5 and

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0.2 per 1,000 patients per year.[1] The incidence of suspected PE, estimated by a survey among Dutch pulmonologists and internists, was 2.6 per 1,000 inhabitants per year, of which about 30% actually had PE.[3] The recurrence of VTE is 7% per year, and 30% of the patients experience a recurrent VTE (RecVTE) event within 8 years.[1,4]

The occurrence of VTE imposes a decreased health-related quality of life and increased costs due to extending hospital stays, additional hospitalizations, and increased case-fatality and mortality rates in patients with PE.[5,6] Although VTE is treated as an acute event, it is associated with an increased risk of recurrence and chronic complications.[1] Post-thrombotic syndrome (PTS) can develop after chronic venous valve insufficiency caused by DVT. A rare delayed complication of PE is chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is caused by arterial lung obstruction, which can induce heart failure.[1]

The current treatment procedure of acute VTE in the Netherlands consists of a minimum of 5 days of low-molecular weight heparin (LMWH), followed by at least 3 months of anticoagulation with a vitamin K antagonist (VKA; eg, warfarin, acenocoumarol, phenprocoumon). Some high-risk patients receive anticoagulants as prophylaxis for a longer period.[3] Although the anticoagulation effect of VKA is considered strongly effective, the use is limited because of increased bleeding risks, a narrow therapeutic range, and the interactions with food and other drugs. Because of the narrow therapeutic range, monitoring of the international normalized ratio (INR) of the prothrombin time of the patients is required. In the Netherlands the INR range for VTE is 2.0 to 3.5, and the monitoring is conducted by specialized thrombotic services.[1–3]

Lately, direct oral anticoagulants (DOACs) have been developed, which address most of these issues. Next to dabigatran, rivaroxaban, and edoxaban, apixaban is one of the representatives of this group of DOACs. Although VKAs inhibit several coagulation factors indirectly, apixaban is a specific factor Xa inhibitor, enabling a more predictable therapeutic effect.[7] Next to this, treatment with apixaban does not require INR monitoring and LMWH use. The AMPLIFY (Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy) trial reported the effectiveness and safety profile of apixaban compared with warfarin in the acute (6 months) treatment of VTE.[8] The trial found noninferiority of apixaban to warfarin in the recurrence VTE or VTE-related death (VTEdie). Moreover, apixaban treatment was associated with a significant reduction of major bleeding (MB) and clinically relevant non-MB. In the AMPLIFY-EXT (for Extended Treatment of Venous Thromboembolism) trial an extended treatment of an additional 6 months of therapy of apixaban in two different doses (2.5 and 5.0 mg) was compared with placebo for the prevention of VTE.[9] Apixaban treatment was found to reduce the risk of RecVTE and VTEdie, without increasing bleeding risks.

With increasing importance of cost-effectiveness in decision making, the consequences for the quality of life and costs associated with apixaban compared with LMWH/VKA need to be considered. This is in particular the case in Western countries, such as the Netherlands.[10] The aim of this study is to estimate the cost-effectiveness of apixaban compared with LMWH/VKA in the acute treatment and secondary prevention of VTE in the Netherlands.

METHODS

Decision Model

The cost-effectiveness of apixaban compared with the current standard treatment of LMWH/VKA was calculated using a cohort-based Markov model designed in Excel (Microsoft, Redman, Washington; 2013).[11,12] A cohort of 1,000 patients who had just experienced a VTE event was followed in the model. The population had an average starting age of 57 years and 59% were male, based on the patient characteristics of the AMPLIFY trial (see **Supplemental Table SI** in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.12.012).[8]

In the Markov model, the patients move through 12 health states: index DVT, index PE, RecVTE (RecPE or RecDVT), VTEdie, MB, CRNM bleed, CTEPH, PTS, treatment discontinuation (TxDiscontinue), other death, and no event. The pathways that specify the transitions among the different health states are detailed in **Figure 1**. A cycle length of 3 months was used, and in each cycle only one event was allowed to occur. The model used half-cycle corrections.[11] Specific event probabilities were based on the AMPLIFY and AMPLIFY-EXT trials and