Evaluation of Oral Anticoagulants for the Extended Treatment of Venous Thromboembolism Using a Mixed-Treatment Comparison, Meta-Analytic Approach

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ABSTRACT

Purpose: Target-specific oral anticoagulants (apixaban, rivaroxaban, and dabigatran) are widely available for the treatment of venous thromboembolism (VTE). Although analyses comparing these agents to placebo or warfarin exist, direct comparisons of these agents for extended VTE treatment have not been conducted. Therefore, this network meta-analysis aimed to evaluate the efficacy and tolerability of VKA and target-specific oral anticoagulants for extended VTE treatment using a mixed-treatment comparison, meta-analytic approach.

Methods: A comprehensive literature search of EMBASE and MEDLINE was conducted to identify relevant randomized, controlled trials published in English between 1960 and November 2013. Eligible studies investigated the extended use ($\geq$6 months) of oral anticoagulants (apixaban, dabigatran, rivaroxaban, and/or warfarin [conventional or low dose]) and placebo in patients with confirmed VTE. Search terms included *extension* or *extended treatment* or *therapy, venous thromboembolism* (or *VTE*), *deep vein thrombosis* (or *DVT*), *pulmonary embolism* (or *PE*), and *anticoagulant* or *anticoagulant agent*. Key articles were cross-referenced for additional studies. The efficacy end points evaluated were recurrent VTE or death from any cause, DVT, and nonfatal pulmonary embolism PE. Tolerability end points included major bleeding and nonmajor or clinically relevant bleeding. The data were screened, evaluated, and entered into statistical software to generate direct and indirect comparisons of the various anticoagulants across each study. The data are reported as rate ratios and 95% credible intervals.

Findings: Ten trials were analyzed and aggregated, representing data from >14,000 patients. With respect to efficacy end points, no statistically significant between-treatment differences in the composite end point of VTE or death, nonfatal PE, or DVT were found. Major bleeding was significantly greater with warfarin versus apixaban (rate ratio, 4.24; credible interval, 1.28–25.0), and the risk for major bleeding varied somewhat with warfarin and greatly with rivaroxaban. The assessment of nonmajor or clinically relevant bleeding did not identify any meaningful differences between these agents.

Implications: The majority of the data represented in this study were derived from noninferiority trials. In the present meta-analysis, efficacy end points in the extended treatment of VTE with apixaban, dabigatran, rivaroxaban, warfarin (conventional and low dose), and placebo were not significantly different. Elevated bleeding risks were identified with rivaroxaban and warfarin; however, the wide credible intervals with rivaroxaban prevent the interpretation of these increased risks. (*Clin Ther*. 2014;36:1454–1464)

Key words: extended treatment, oral anticoagulant, recurrent venous thromboembolism, venous thromboembolism, VTE.

INTRODUCTION

Venous thromboembolism (VTE) is mainly composed of lower and upper extremity deep vein thrombosis (DVT) and pulmonary embolism (PE), which have a combined annual incidence of 1 to 2 events per 1000

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population in the United States.[1,2] The annual recurrence rate after a first VTE episode is between 3% and 12%, depending on the index event (proximal or distal DVT, or PE); etiology (provoked or idiopathic); and the presence of risk factors such as previous VTE, thrombophilia, and active cancer.[3,4]

Current practice guidelines recommend VTE treatment for ≥3 months after an initial event; however, patients at increased risk for recurrent events may require extended treatment.[5] Warfarin is a vitamin K antagonist (VKA) used for the extended treatment of VTE, although the optimal treatment duration is unknown. Extended VTE treatment with VKA increases major bleeding risk by 1% to 2% and thus an assessment of each patient's potential for treatment-related bleeding and risk for recurrent VTE should be considered. Furthermore, each patient's values, preferences, and abilities should be considered in shared decisions about alternative anticoagulation therapy.[5,6]

There are some inherent challenges when initiating warfarin therapy. First, parenteral anticoagulants are used with warfarin because 5 to 7 days are required to adequately deplete vitamin K reserves and thereby reduce the synthesis of active clotting factors.[5] The need for parenteral anticoagulation can lead to increased length of hospitalization, utilization of various health care resources, and costs.[7,8] Moreover, warfarin requires frequent laboratory monitoring and dose adjustments due to pharmacogenomic considerations, as well as food, disease, and drug interactions. The introduction of target-specific oral anticoagulants (direct Xa inhibitors [apixaban, rivaroxaban], direct thrombin inhibitor [dabigatran]) allows some of these issues to be avoided because these classes have faster onset and, to date, fewer known drug interactions requiring modification of therapy as a tolerability concern. A direct and adjusted, pair-wise meta-analysis of Phase II and III trials evaluated the efficacy and tolerability of the target-specific oral anticoagulants compared with VKA in the acute treatment of VTE and reported no reductions in the rates of recurrent VTE compared with VKA, although the rate of major bleeding was lower with rivaroxaban compared with VKA.[9] Few patients receiving apixaban were represented in that analysis, and more data have since become available.

In the absence of large-scale, head-to-head studies of target-specific oral anticoagulants as active comparators, we conducted a mixed-treatment comparison, network meta-analysis, using direct and indirect comparisons, on the latest data from the few available trials of VKA and target-specific oral anticoagulants to evaluate their effectiveness and tolerability in the extended treatment of VTE.

MATERIALS AND METHODS

This analysis evaluated the efficacy and tolerability of 4 oral anticoagulants in the extended treatment of VTE: apixaban, dabigatran, rivaroxaban, and warfarin (including low-intensity warfarin, with a target international normalized ratio [INR] of 1.5–2, and conventionally dosed warfarin, using a target INR of 2–3). We evaluated a composite efficacy end point of recurrent VTE or death from any cause, and single end points of DVT and nonfatal PE. Pertinent tolerability end points included investigator-defined major bleeding and a composite end point of nonmajor or clinically relevant bleeding (**Table I**).

A comprehensive literature search of EMBASE and MEDLINE was conducted for all randomized, controlled trials of oral anticoagulants in the extended treatment of VTE published from 1960 to November 2013. Key terms used in the search included *extension* or *extended treatment* or *therapy, venous thromboembolism* (or *VTE*) or *deep vein thrombosis* (or *DVT*) or *pulmonary embolism* (or *PE*), *anticoagulant* or *anticoagulant agent, apixaban* (or *Eliquis), rivaroxaban* (or *Xarelto), dabigatran* (or *Pradaxa*), *and warfarin* (or *vitamin K antagonist*). Key articles were cross-referenced for additional studies. Studies were included in the analysis if they enrolled patients aged ≥15 years with a history of ≥1 VTE episode and who received anticoagulation therapy for a minimum duration of 6 months (**Table II**). Trials were excluded if they did not meet the prespecified criteria; assessed oral treatments that were not considered the standard of care, such as aspirin; evaluated prophylactic doses; and/or evaluated a parenteral anticoagulant. Given these criteria, studies examining apixaban, dabigatran, rivaroxaban, warfarin, and placebo were included in the analysis (see the **Supplemental Table I** in the online version at http://dx.doi.org/10.1016/j.clinthera.2014.06.033). Each author reviewed each study to evaluate the methodology and patients' characteristics and to assign quality (Jadad) scores by assessing randomization, blinding, and allocation concealment. Intrarater reliability was assessed (Fleiss κ, 0.93) and discrepancies were resolved with additional review and discussion.[10]