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Treatment Discontinuations With New Oral Agents for Long-term Anticoagulation: Insights From a Meta-analysis of 18 Randomized Trials Including 101,801 Patients

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Abstract

Objective: To systematically examine discontinuation rates with new US Food and Drug Administration–approved oral anticoagulants (NOACs) in patients with various indications for long-term anticoagulation.

Patients and Methods: Poor adherence to medications is considered a potential and frequent cause of treatment failure. We searched the PubMed, Cochrane Central Register of Controlled Trials, EMBASE, EBSCO, Web of Science, and CINAHL databases for articles published from January 1, 2001, through September 15, 2013. The following Medical Subject Heading terms and/or keywords were used for our database searches: *rivaroxaban*, *dabigatran*, *apixaban*, *new oral anticoagulants*, *oral thrombin inhibitors*, and *oral factor Xa inhibitors*. Articles in English that focused on randomized controlled trials (RCTs) comparing NOACs (apixaban, dabigatran, and rivaroxaban) with conventional therapy or placebo were abstracted. Independent extraction of relevant data was performed by 2 authors. The primary end point of interest was discontinuation due to all causes. Other end points of interest were discontinuation due to adverse events, consent withdrawal, and nonadherence.

Results: Eighteen RCTs including a total of 101,801 patients were included for analysis. Total study drug discontinuation rates were not statistically different with NOACs in comparison to pharmacologically active comparators for treatment of venous thromboembolism/pulmonary embolism (risk ratio [RR], 0.91; 95% CI, 0.74-1.13; P=.40) and for NOACs in comparison to warfarin and aspirin for prevention of stroke in patients with atrial fibrillation (RR, 1.01; 95% CI, 0.87-1.17; P=.92). In contrast, in acute coronary syndromes, total study drug discontinuation with NOACs was significantly higher than with placebo (RR, 1.40; 95% CI, 1.07-1.83; P=.01). Overall discontinuations were comparable to those with active comparators.

Conclusion: Study drug discontinuations with NOACs were not significantly different from those with conventional drugs in treatment of venous thromboembolism/pulmonary embolism and prevention of stroke in patients with atrial fibrillation but were worse in acute coronary syndromes as noted in evidence from contemporary RCTs.

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Poor adherence to medications is considered to be a potential cause of treatment failure.[1] Previous studies have reported that adherence to effective therapy translated into positive health outcomes and lower mortality.[1] Nonadherence is more common in long-term therapy for chronic diseases than in short-term therapy for acute conditions.[2] Nonadherence to conventional anticoagulants such as vitamin K antagonists (VKAs) has been associated with inadequate anticoagulation and high risk of embolic events.[3] The new oral anticoagulants (NOACs) dabigatran, rivaroxaban, and apixaban have been evaluated in several indications for long-term anticoagulation such as stroke prevention in atrial fibrillation (AF), treatment of venous thromboembolism (VTE), and acute coronary syndrome (ACS).[4-6]

The NOACs have efficacy and safety comparable to that of VKAs for stroke prevention

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in AF and for treatment of VTE.[4,6] They have certain potential advantages over VKA, such as rapid onset of action, obviation of need for bridging therapy with heparin, predictable effects with fixed dosages, and no need for monitoring.[4,6] However, there is concern regarding poor adherence with these newer anticoagulant agents in recent publications.[4,7,8] Several randomized controlled trials (RCTs) have reported high discontinuation rates with these new oral agents.[9-11] Previous reports suggest that higher doses may be required to achieve similar levels of anticoagulation efficacy for the same drug in patients with poor adherence to new anticoagulants.[7] The NOACs with twice-daily doses, dabigatran and apixaban, may have higher rates of nonadherence because of the increased frequency of medication administration.[7,8] Adherence is essential for these drugs to be effective without causing major complications.[12-14] However, data related to discontinuation of NOACs is sparse and heterogeneous in published studies, and various causes of drug discontinuation have not been examined for a comprehensive evaluation. We conducted a meta-analysis to examine the discontinuation rates of NOACs for various indications for long-term anticoagulation.

PATIENTS AND METHODS

Data Sources and Searches

We searched the PubMed, Cochrane Central Register of Controlled Trials, EMBASE, EBSCO, Web of Science, and CINAHL databases from January 1, 2001, through September 15, 2013, for English-language, peer-reviewed publications. We identified RCTs with the NOACs dabigatran, rivaroxaban, and apixaban for long-term anticoagulation (more than 12 weeks because that remains the minimum duration of treatment recommended for thrombotic events) for various indications. The following Medical Subject Heading terms and/or keywords were used for our database searches: *rivaroxaban*, *dabigatran*, *apixaban*, *new oral anticoagulants*, *oral thrombin inhibitors*, and *oral factor Xa inhibitors*. We also searched related reviews, clinical trials databases, and the reference lists of all retrieved articles.

Study Selection

We included RCTs that compared NOACs with conventional anticoagulants or placebo for the treatment of VTE/pulmonary embolism (PE), ACS, and stroke prevention in patients with AF. The included studies had to have at least 12 weeks of follow-up. We did not include studies of orthopedic operations because of the considerably shorter durations of treatment and follow-up, the greater variability in baseline characteristics, and surgery-specific confounding factors. Both double-blind and open-label trial designs were eligible for inclusion. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement for reporting of systematic reviews and meta-analyses of RCTs[15] was followed for the protocol of our meta-analysis (Figure 1).

Data Extraction and Quality Assessment

Two physician-reviewers (S.C., P.S.) independently extracted data from relevant published articles after determining the eligibility for inclusion. Disagreements regarding data incorporation were resolved by consensus among all authors. Methods specified in the *Cochrane Handbook for Systematic Reviews of Interventions*[16] were followed for objective assessment of the included trials. We extracted data from published sources regarding total number of treated patients, duration of follow-up, and drugs for the intervention and control groups. The occurrence of the following 4 end points was abstracted according to the intention-to-treat population for individual trials and separately for the study drug and control drug: discontinuation due to all causes, discontinuation due to adverse events, discontinuation due to consent withdrawal, and discontinuation due to nonadherence. The definition for each end point was that specified by the individual trial (details of the definitions are provided in the Supplemental Appendix, available online at http://www.mayoclinicproceedings.org).

Data Synthesis and Analysis

To combine the data from each study, random-effects (DerSimonian and Laird) models (as appropriate for using data from published literature) were used to calculate a summary estimate of discontinuation across all included studies. When more than one dose of the study drug was used in a single trial, we added the data related to particular end points for all doses, ie, we added the discontinuation events for different doses of the NOACs and used the