CLINICAL RESEARCH STUDY

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Efficacy and Safety Outcomes of Direct Oral Anticoagulants and Amiodarone in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND: Direct oral anticoagulants (DOACs) and amiodarone are widely used in the treatment of nonvalvular atrial fibrillation. The DOACs are P-glycoprotein (P-gp) and cytochrome p-450 (CYP3A4) substrates. Direct oral anticoagulant levels may be increased by the concomitant use of potent dual P-gp/CYP3A4 inhibitors, such as amiodarone, which can potentially translate into adverse clinical outcomes. We aimed to assess the efficacy and safety of drug–drug interaction by the concomitant use of DOACs and amiodarone.

METHODS: We performed a systematic review of MEDLINE, the Cochrane Central Register of Clinical Trials, and Embase, limiting our search to randomized controlled trials of patients with atrial fibrillation that have compared DOACs versus warfarin for prophylaxis of stroke or systemic embolism, to analyze the impact on stroke or systemic embolism, major bleeding, and intracranial bleeding risk in patients with concomitant use of amiodarone. Risk ratio (RR) 95% confidence intervals were measured using the Mantel-Haenszel method. The fixed effects model was used owing to heterogeneity (I^2) < 25%.

RESULTS: Four trials with a total of 71,683 patients were analyzed, from which 5% of patients (n = 3212) were concomitantly taking DOAC and amiodarone. We found no statistically significant difference for any of the clinical outcomes (stroke or systemic embolism [RR 0.85; 95% CI, 0.67-1.06], major bleeding [RR 0.91; 95% CI, 0.77-1.07], or intracranial bleeding [RR 1.10; 95% CI, 0.68-1.78]) among patients taking DOAC and amiodarone versus DOAC without amiodarone.

CONCLUSION: On the basis of the results of this meta-analysis, co-administration of DOACs and amiodarone, a dual P-gp/CYP3A4 inhibitor, does not seem to affect efficacy or safety outcomes in patients with atrial fibrillation.

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KEYWORDS: Amiodarone; Atrial fibrillation; Cytochrome p450; Direct oral anticoagulants; Intracranial bleeding; Major bleeding events; P-glycoprotein; Stroke

The introduction of direct oral anticoagulants (DOACs)—apixaban, dabigatran, edoxaban, and rivaroxaban—has significantly impacted the anticoagulation management of nonvalvular atrial fibrillation. Patients treated with DOACs have similar efficacy outcomes, fewer adverse events, greater compliance, and an improved quality of life when compared with those treated with vitamin K antagonists (VKAs).[1,2] However, certain questions remain

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regarding common drug–drug interactions with these medications.

Despite a high incidence of side effects and drug–drug interactions, amiodarone is the most commonly prescribed antiarrhythmic drug for patients with atrial fibrillation. This is due to its superior antiarrhythmic and atrioventricular nodal blocking effects in comparison with other antiarrhythmic drugs.[3] Amiodarone is a cytochrome p-450 3A4 (CYP384) inhibitor and a P-glycoprotein (P-gp) inhibitor, and thus it affects the plasma concentration of a wide range of concomitantly prescribed medications, including VKAs (coumadin).[4,5] The impact of amiodarone on the efficacy and safety of DOAC administration is less clear. With greater adoption of DOACs, a body of literature has been produced, in which patients are taking both amiodarone and a DOAC medication. We aimed to assess the efficacy and safety profile of the DOACs when used concomitantly with amiodarone in patients with atrial fibrillation by a systematic review of the literature and subsequent meta-analysis.

CLINICAL SIGNIFICANCE

- In patients with nonvalvular atrial fibrillation taking a direct oral anticoagulant (DOAC), co-administration of amiodarone does not seem to affect the rates of stroke or systemic embolism, major bleeding, or intracranial bleeding when compared with DOAC use alone.

METHODS

Search Strategy

We searched PubMed, Embase, and the Cochrane Central Register of Clinical Trials (Cochrane Library, Issue 09, 2017). This was assessed up to September 2017. No language restriction was applied. The reference lists or bibliographies of identified articles were also reviewed. Search terms included *(Atrial Fibrillation OR Stroke Risk OR Bleeding Risk) AND (Dabigatran OR Rivaroxaban OR Edoxaban OR Apixaban OR Warfarin OR Vitamin K antagonist OR Amiodarone).*

Selection Criteria

The PRISMA statement for reporting systematic reviews and meta-analyses was applied to the methods for this study.[6] The studies had to fulfill the following criteria to be included in the analysis: 1) our analysis was restricted to randomized controlled trials (RCTs) that included patients with nonvalvular atrial fibrillation who were assigned to receive DOACs or VKAs; 2) trials had to have included efficacy and safety outcomes as part of their respective analyses; and 3) trials had to report the use of amiodarone among the trial cohort and its influence on the analyzed outcomes.

Study Endpoints

We compared the efficacy (stroke and/or systemic embolism rates) and safety (major bleeding and intracranial bleeding) in patients concomitantly using DOACs and amiodarone versus patients taking DOACs but not amiodarone.

Data Extraction

Two authors (FL and CM) searched the studies and extracted the data independently and in duplicate. The information about the following outcomes was extracted from the original manuscripts, supplementary data, and separate post hoc analyses. Information was gathered using standardized protocol and reporting forms. Disagreements were resolved by consensus. Two reviewers (FL and CM) independently assessed the quality items, and discrepancies were resolved by consensus.

Individual Study Quality Appraisal

Two authors (FL and CM) independently assessed the risk of bias of included trials using standard criteria defined in the *Cochrane Handbook for Systematic Reviews of Interventions*.[7,8] This validated instrument for appraising randomized trials measures risk of bias in 7 categories: 1) adequate random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective reporting, and 7) other bias. Each trial is described as having a high, low, or unclear risk of bias in each of the 7 domains. Discrepancies were resolved by discussion or adjudication by a third author (JR).

Statistical Analysis

Data were summarized across treatment arms using the Mantel-Haenszel risk ratio (RR). We evaluated heterogeneity of effects using the Higgins I^2 statistic.[8] We used fixed effects models for analyses with low heterogeneity (defined as $I^2 < 25\%$); otherwise, random effects models of DerSimonian and Laird were used.[9] To address publication bias, we performed funnel plot analyses.[10] We performed a separate sensitivity analysis, assessing the effect of amiodarone exclusively on direct factor Xa inhibitors by performing a meta-analysis that excluded trials using thrombin inhibitors. Descriptive statistics are presented as means and standard deviations for continuous variables or number of cases and percentages for dichotomous and categorical variables. The statistical analysis was performed by RevMan, version 5.3 (2014; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

RESULTS

Study Selection

Study selection is outlined. We identified 2429 abstracts, of which 1024 abstracts were retrieved and reviewed for possible inclusion. Twenty full-text manuscripts were assessed for eligibility; of these, 13 studies were not RCTs. Another study was excluded because it did not include amiodarone use data (**Figure 1**).[11] We included in our final analysis 4 RCTs