Drug Class, Renal Elimination, and Outcomes of Direct Oral Anticoagulants in Asian Patients: A Meta-Analysis

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Background: Direct oral anticoagulants (DOACs) have a better risk benefit profile in Asian patients with atrial fibrillation (AF). Whether treatment effects could be modified by drug class and dependency on renal elimination of studied agents has not yet been explored. *Methods:* We searched PubMed, CENTRAL, and CINAHL databases through November 2016 for phase III randomized controlled trials comparing DOACs with warfarin in patients with AF. Efficacy and safety outcomes were pooled according to drug class and dependency on renal elimination of DOACs and were compared with the Mantel-Haenszel fixed-effects model. Effect differences were assessed with Bucher's indirect comparisons using common estimates, once heterogeneity was low, and with the Bayesian method. *Results:* Among 6496 Asian patients from 6 trials, both direct thrombin inhibitors and factor Xa inhibitors, compared with warfarin, were associated with lower risks of stroke or systemic embolism and major bleeding (risk ratio [95% confidence interval], 0.51 [0.33-0.78], 0.74 ([0.58-0.96], 0.60 [0.41-0.86], and 0.59 [0.47-0.76], respectively). There was no between-group difference in direct thrombin inhibitors and factor Xa inhibitors or in DOACs with renal elimination less than 50% and 50% or greater (all $I^2 < 25\%$ and interaction $P > .05$). Indirect comparisons within strata of drug class and dependency on renal elimination showed no preferential effect of any given regimen over another. There was no difference in effects on ischemic and hemorrhagic stroke, intracranial hemorrhage, myocardial infarction, and all-cause mortality

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between DOACs stratified by pharmacologic characteristics. *Conclusions:* DOACs, as a therapeutic class, outperform warfarin in efficacy and safety in Asian patients with AF. **Key Words:** Anticoagulants—Asian patients—atrial fibrillation—direct thrombin inhibitors—factor Xa inhibitors.

Introduction

In patients with atrial fibrillation (AF), warfarin effectively prevents ischemic stroke and reduces mortality.[1] Notwithstanding evidence-based advocacy emphasizes the essential role of anticoagulation treatment in AF management, the risk of excessive bleeding and inconvenient features carried by warfarin preclude its widespread use. That is particularly true in Asia, where it has been widely perceived that inherent susceptibility of Asian patients to warfarin results in unacceptably high rates of major bleeding and intracranial hemorrhage (ICH).[2]

The development of ximelagatran, the first direct oral anticoagulant (DOAC), is groundbreaking for stroke prevention in patients with AF by introducing an oral fixed-dose regimen that directly inhibits a single coagulation step and needs no routine coagulation monitoring. Recent phase III randomized controlled trials (RCTs) of 4 new DOACs further suggest that these agents share important similarities as they are as effective as well-managed warfarin while carrying a lower risk of ICH.[3,4] Moreover, DOACs have an even better risk benefit profile in Asian patients than in non-Asian patients.[5] Nevertheless, dissimilarities in efficacy and safety between these agents have been observed.[6-8] Despite differences that might be attributed to trial designs and patients characteristics, whether pharmacologic characteristics of individual DOACs are accountable for those observations in Asian patients are largely unexplored, particularly as Asian patients enrolled in RCTs, compared with non-Asian patients, had lower body weight and creatinine clearance,[9-12] propensities to overexposure to studied agents.

In this meta-analysis, we aimed to assess associations between pharmacologic characteristics of DOACs (stratified by drug class and dependency on renal elimination) and treatment outcomes using indirect comparisons and network meta-analyses of phase III RCTs of DOACs in patients with AF because head-to-head long-term outcome trials are lacking to fill this knowledge gap.

Method

Data Source and Search

We searched PubMed, CENTRAL, and CINAHL databases for phase III RCTs (through November 2016) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Terms used for the search included AF, apixaban, dabigatran, edoxaban, rivaroxaban, and ximelagatran. In addition, to ensure a comprehensive literature search, reference lists of published meta-analyses and reviews were reviewed. Complementary information of aforementioned DOACs was searched in the website of the regulatory agency.

Eligibility Criteria

We included RCTs that (1) compared any of DOACs with dose-adjusted warfarin (targeted international normalized ratio of 2.0-3.0) in patients with non-valvular AF and (2) reported long-term (≥1 year) efficacy and safety in Asian patients. Phase II RCTs and RCTs in the setting of interventions (e.g., catheter ablation or cardioversion for AF) were not eligible.

Data Extraction and Quality Assessment

Two authors (K.-L.W. and C.-Y.L.) independently evaluated studies for possible inclusion and non-relevant studies were excluded after reviewing titles and abstracts. For potentially relevant studies, full-text papers were retrieved. The eligibility assessment and data extraction using a standardized protocol were performed independently. Information on study characteristics (designs, sample sizes, numbers of Asian patients, and the quality of warfarin management) and efficacy and safety outcomes were collected. If outcome data were reported in multiple publications or populations, we used the following hierarchy of data sources: the first report of the intention-to-treat population in peer-reviewed papers, then public reports from the regulatory agency. Risks of bias were assessed using the Risk of Bias Tool developed by the Cochrane Collaboration. Disagreements between 2 authors were resolved by discussion.

Definition of Asian Patients

Because individual patient data were not available, we could not ascertain the ethnicity of each patient enrolled in RCTs. Thus, we used the country of residence reported as a surrogate for the ethnicity.

Data Synthesis and Analysis

Information of Asian patients enrolled in RCTs comparing ximelagatran with warfarin was scarce in published literatures because ximelagatran was withdrawn from the market. We can retrieve only limited data from the regulatory agency and therefore outcomes other than primary efficacy and safety with ximelagatran in Asian patients