Use of Direct Oral Anticoagulants in Special Populations

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KEYWORDS

• DOAC • Anticoagulation • Venous thromboembolism • Atrial fibrillation

KEY POINTS

- Although direct oral anticoagulants (DOACs) represent an excellent alternative to warfarin in venous thrombosis or atrial fibrillation, some patient populations were not well-represented in individual clinical trials.
- For patients with extremes of body weight, advanced age, or moderate renal insufficiency, some DOACs may be preferred over warfarin and others may be less attractive.
- The choice and dosing of DOACs in selected populations is complex and must be individualized.
- More evidence about the safety and effectiveness of DOACs are needed in highly pro-thrombotic states, such as cancer and antiphospholipid syndrome.

INTRODUCTION

Although direct oral anticoagulants (DOACs) have been approved for the treatment of venous thromboembolism (VTE) and atrial fibrillation (AF) in the United States based on phase III randomized controlled trials (RCTs) that have directly compared with vitamin K antagonists (VKAs), questions remain about their applicability and safety in selected populations that were less represented in the trials. With rare exceptions, DOACs have been studied and approved using a "one-dose-fits-all" model, without

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the need for routine measurement of anticoagulant effect. Although this simplicity is attractive, in some situations, the absence of an evidence based dose adjustment algorithm can be problematic. In this article, we review the currently available evidence relevant to the use of DOACs in patients with extremes of body weight, advanced age, renal impairment, cancer, and antiphospholipid antibody syndrome (APS). When presenting data derived from individual or pooled subgroup analyses, both the interaction effects and the sample sizes within these subgroups are important. In **Table 1** we present the names of the major phase III VTE and AF trials, their relevant dosing, as well as the sample size for each subgroup. In this review, we will focus on the US Food and Drug Administration (FDA)–approved dosing when more than 1 dose has been studied for a particular DOAC.

PATIENTS AT EXTREMES OF BODY WEIGHT

Patients with extreme body weight are common in clinical practice. Obesity is an independent risk factor for both VTE and AF.[1–3] Alternatively, patients with low body weight may have higher risk of bleeding with all forms of anticoagulation. Pharmacokinetic and pharmacodynamic studies in healthy subjects suggest that overall DOAC exposure for patients at extremes of body weight (<50 or >120 kg) is not substantially different from the exposure in patients who weigh between 50 and 120 kg.[4–7] However, few patients with weight 50 kg or less or greater than 120 kg were included in phase III RCTs. While there is a metaanalysis comparing the efficacy and risks of DOACs versus VKA using data from the VTE (not AF) trials, the authors compared "clinically relevant" rather than "major bleeding" risks as a clinical outcome and there was significant variation of the definition of "high" and "low" body weight depending on the individual trial.[8] In this section, we review data from subgroups of phase III AF and VTE trials to compare the rates of thrombosis and major bleeding for DOACs versus VKA in patients with extremes of body weight (**Table 2**).

According to the package insert, dabigatran trough concentration is 20% lower in subjects with a body weight of greater than 100 kg.[4] In a pooled analysis of the Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism (RE-COVER) studies (see **Table 1**), dabigatran 150 mg versus warfarin had a consistent treatment effect on primary efficacy in both high (>100 kg) and low (≤50 kg) body weight subgroups (nonsignificant interactions).[9,10] Of note, there were only 57 patients with weight 50 kg or less and the number of patients with weight greater than 120 kg was not reported; thus, these results must be applied to these subgroups with caution. Major bleeding was not reported as a subgroup outcome. In the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, subgroup analysis for dabigatran 150 mg versus warfarin based on weight was also consistent with the primary trial for both improved primary efficacy and noninferior major bleeding (nonsignificant interactions).[11,12] This result was confirmed by a recently published subgroup analysis where no significant interaction was observed for the relative effect of dabigatran versus warfarin on stroke or bleeding rates when patients were stratified into top 10% and bottom 10% of body mass index (BMI).[13]

When given to healthy volunteers, the area under the curve (AUC) for rivaroxaban was not significantly different ($P = .21$) for healthy subjects who weighed 50 kg or less or more than 120 kg when compared with those who weighed 70 to 80 kg.[5] In a pooled analysis of the 2 Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis (EINSTEIN) VTE studies, there were only 107 patients with body weight of 50 kg or less.[14] In this low body weight