Letters to the Editor

Clarification for Apixaban Dosing in Patients with Impaired Renal Function

Original Article: Deep Venous Thrombosis and Pulmonary Embolism: Current Therapy

Issue Date: March 1, 2017

See additional reader comments at: https://www.aafp.org/afp/2017/0301/p295.html

To the Editor: We thank the authors for a very well-written and thorough review of the current treatment landscape for deep venous thrombosis and pulmonary embolism. *Table 1* reviews direct oral anticoagulant dosing, including renal dose adjustments. Apixaban (Eliquis) renal dosing was included as 2.5 mg orally twice daily if at least one criterion is met: serum creatinine 1.5 mg per dL (133 µmol per L) or more, age 80 years or older, or weight 60 kg (132 lb, 4 oz) or less. The AMPLIFY trial looked at apixaban for treatment of deep venous thrombosis/pulmonary embolism and excluded patients with a serum creatinine level of 2.5 mg per dL (221 µmol per L) or greater, or a creatinine clearance less than 25 mL per minute per 1.73 m^2 (0.42 mL per second per m^2).[1] On the other hand, per the manufacturer, no dosage adjustment is required for renal function, although it is noted that patients with a creatinine clearance less than 15 mL per minute per 1.73 m^2 (0.25 mL per second per m^2) and patients on dialysis were not included in clinical trials; all the conclusions we drew from the literature regarding these patients were based on pharmacokinetic and pharmacodynamic (anti–factor Xa activity) data.[2,3] The dosing the authors list in *Table 1* is most similar to dosing guidelines for reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. However, that recommendation requires an adjustment to the 2.5-mg dose when two of the three criteria are met based on the ARISTOTLE and AVERROES trials.[4,5] Given this contradictory information, we would appreciate some clarification on the need to adjust apixaban dosing in patients with impaired renal function.

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In Reply: Thank you for your inquiry regarding our article. In *Table 1*, we recommended modified dosing of apixaban (2.5 mg twice daily) if at least one of the following criteria is met: serum creatinine 1.5 mg per dL (133 µmol per L) or greater, age 80 years or older, weight 60 kg (132 lb, 4 oz) or less. However, as Drs. Naik and Ragheb correctly state, the manufacturer does not recommend any adjustment for renal insufficiency, age, or weight when treating venous thromboembolism.[1] According to the U.S. Food and Drug Administration, no renal adjustment is necessary for apixaban when used to treat venous thromboembolism, even in patients with end-stage renal disease and/or patients on hemodialysis.[2]

To our knowledge, the only clinical trial that addresses the question of apixaban use for venous thromboembolism in patients with impaired renal function is the AMPLIFY study.[3] Patients were

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excluded from the study if the serum creatinine level was greater than 2.5 mg per dL (221 µmol per L) or the calculated creatinine clearance was less than 25 mL per minute per 1.73 m^2 (0.42 mL per second per m^2). However, no dosage adjustments were made for patients in the study with mild renal dysfunction.

Upon further consideration and to provide a recommendation that is most consistent with current knowledge, we would like to remove our recommendation for dose adjustment of apixaban. However, we recommend careful monitoring for any patient prescribed apixaban for venous thromboembolism whose renal function falls outside of the population that was studied in clinical trials.

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Treatment of Venous Thromboembolism in Patients Who Are Morbidly Obese

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To the Editor: We read the article on venous thromboembolism (VTE) with interest and appreciate that the authors highlight the different

treatment options for this disease state. Given the limited data regarding treatment of VTE in patients who are morbidly obese (body mass index [BMI] of 40 kg per m^2 or more) and that the current prevalence of morbid obesity in the United States is around 8%,[1] family physicians must keep weight and BMI in mind when considering direct oral anticoagulants and low-molecular-weight heparin (LMWH) for VTE treatment.

The International Society on Thrombosis and Haemostasis offers some guidance.[2] Standard dosing of direct oral anticoagulants should still be considered for VTE prevention and treatment for patients with a BMI less than or equal to 40 kg per m^2 or weight less than or equal to 264 lb (120 kg). For patients with a BMI greater than 40 kg per m^2 or weight more than 120 kg, direct oral anticoagulants should not be considered a first-line therapy because of limited clinical data and evidence suggesting decreased exposure, concentration, and half-lives at the weight extremes.

However, the International Society on Thrombosis and Haemostasis suggests that for patients who are morbidly obese who cannot use a vitamin K antagonist (warfarin [Coumadin]), physicians might consider checking anti–factor Xa peak and trough levels (for apixaban [Eliquis], edoxaban [Savaysa], and rivaroxaban [Xarelto]). It should be noted that all data regarding anti–factor Xa levels used tests specifically calibrated for the drug being tested or mass spectrometry drug levels. Continuing the direct oral anticoagulant is reasonable if the level falls within the expected range, but changing to a vitamin K antagonist is recommended, if possible, if the drug level is below the therapeutic range.[2]

If a vitamin K antagonist and bridging with LMWH is used, it is also important to note the limited data and different pharmacokinetic and pharmacodynamic properties in patients who are morbidly obese. The LMWH agent enoxaparin (Lovenox) has no official dosing recommendations for these patients,[3] but data in this population suggest that a reduced weight-based dose (less than 1 mg per kg) is warranted.[4,5] A retrospective cohort of 99 patients with BMI greater than 40 kg per m^2 or weight more than 331 lb (150 kg) showed that more than 50% of patients had supratherapeutic peak anti–factor Xa levels using normal weight-based dosing of 1 mg per kg of enoxaparin.[4] A prospective dosing study also showed an average enoxaparin dose of 0.71 mg per kg for therapeutic effects.[5] Therefore, it is also important for physicians to consider starting LMWH at lower doses and consider monitoring peak anti–factor Xa concentrations in patients who are morbidly obese.

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In Reply: We thank Drs. Gibbs and Sheley for raising an important issue regarding our article. We agree that direct oral anticoagulant use in patients with a BMI greater than 40 kg per m^2 has not been adequately studied and should be avoided. Although monitoring peaks and troughs in anti–factor Xa levels in patients who are morbidly obese and treated with factor Xa inhibitors may help safely guide therapy in this population, these laboratory assays are not readily available to most family physicians. In our experience, treatment of acute VTE in patients who are morbidly obese is most safely achieved by using intravenous unfractionated heparin and concomitant warfarin.

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