REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Renal Function and Direct Oral Anticoagulant Treatment for Venous Thromboembolism

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ABSTRACT

Because differences in renal function can affect the efficacy and safety of direct oral anticoagulants, prescribing an appropriate dose based on renal function is critical, especially in patient populations with a high incidence of renal impairment. In patients with nonvalvular atrial fibrillation and mild or moderate renal impairment, direct oral anticoagulants are associated with a better risk–benefit profile compared with warfarin. However, less is known regarding outcomes in patients with venous thromboembolism and renal impairment. The efficacy and safety of direct oral anticoagulants in patients with venous thromboembolism and renal impairment are primarily derived from prespecified subgroup analyses of the phase 3 clinical trials. We summarize the available data on direct oral anticoagulant use in patients with venous thromboembolism and renal impairment. Clinicians are encouraged to follow study inclusion/exclusion criteria and perform renal dose adjustments based on the Cockcroft–Gault equation using actual body weight when indicated to avoid adverse events.

 • The American Journal of Medicine (2017) 130, 1137–1143

KEYWORDS: Direct oral anticoagulants; Renal; Venous thromboembolism

INTRODUCTION

Venous thromboembolism, which includes deep vein thrombosis and pulmonary embolism, is a significant healthcare concern, with an estimated annual incidence of 1 to 2 per 1000 person-years.[1] Vitamin K antagonists with initial heparin treatment have long been considered a mainstay for the management of venous thromboembolism.[2] However, direct oral anticoagulants such as the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors apixaban, rivaroxaban, and edoxaban have more predictable pharmacodynamics and require less routine laboratory monitoring compared with vitamin K antagonists.[3] In addition, direct oral anticoagulants as a class have similar efficacy and are associated with less bleeding than vitamin K antagonists for the treatment of acute venous thromboembolism.[4] Because of their advantages, direct oral anticoagulants are now recommended over vitamin K antagonists for the management of venous thromboembolism in patients without cancer.[5] Randomized trials are under way evaluating edoxaban, apixaban, and rivaroxaban versus low-molecular-weight heparin in the cancer patient with venous thromboembolism (NCT02073682, NCT02585713, NCT02742623, NCT02583191).

All direct oral anticoagulants have some dependence on renal clearance; therefore, differences in renal function can affect their efficacy and safety.[6-9] Prescribing the appropriate dose based on renal function is critical, especially in patient populations with a high incidence of renal impairment, including the elderly, hospitalized patients, and patients with cancer.[10-12] The prevalence of chronic kidney disease in the

Funding: Funding for writing and editorial support was provided by Daiichi Sankyo.

Conflicts of Interest: CEM has served as a consultant for Portola, Point of Care Software Solutions, Daiichi Sankyo, Sanofi-Aventis, Boehringer Ingelheim, Johnson & Johnson, Polymedix Inc, LEO Pharma, and Eisai; and served as a speaker for Janssen, Bristol-Myers Squibb, Pfizer, Sanofi-Aventis, Portola, and Boehringer Ingelheim. JF has served as a consultant for Boehringer Ingelheim and Portola. PPD has served as a consultant for Janssen, Daiichi Sankyo, Pfizer, Bristol-Myers Squibb, and Boehringer Ingelheim.

Authorship: All authors were involved in writing the manuscript, had full control of content, and have seen and approved the submitted version.

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0002-9343/$ - see front matter
http://dx.doi.org/10.1016/j.amjmed.2017.06.004

United States is 10% to 14% and possibly increasing.[13,14] Thus, physicians likely will be faced with decisions regarding the management of venous thromboembolism in patients with renal insufficiency in clinical practice.

In patients with nonvalvular atrial fibrillation and mild or moderate renal impairment, direct oral anticoagulants are associated with a better risk–benefit profile compared with warfarin.[15] However, less is known regarding outcomes in patients with venous thromboembolism and renal impairment.

CLINICAL SIGNIFICANCE

- The direct oral anticoagulants are noninferior to warfarin in preventing recurrent venous thromboembolism and are associated with a lower bleeding risk in patients with normal renal function.
- Clinicians are encouraged to follow study inclusion/exclusion criteria and perform renal dose adjustments based on Cockcroft–Gault using actual body weight when indicated to avoid adverse events.

VENOUS THROMBOEMBOLISM AND RENAL IMPAIRMENT

Patients with renal impairment have an increased incidence of venous thromboembolism compared with those with normal renal function.[16,17] Further, a low estimated glomerular function is an independent predictor of venous thromboembolism.[17,18] In addition, patients with chronic kidney disease have a higher incidence of upper-extremity deep vein thrombosis compared with patients with normal renal function.[19] In patients with chronic kidney disease, the risk of venous thromboembolism is highest within the first 3 months after chronic kidney disease diagnosis.[20]

In a medical record review of patients with venous thromboembolism at 2 Canadian hospitals, normal renal function was present in only 48% of patients, whereas 47% had mild-to-moderate renal function and 5% had severe renal impairment.[21] Likewise, in a retrospective chart review in 6 German hospitals, approximately 11% of 5710 patients with venous thromboembolism had an estimated glomerular rate <30 mL/min and 40.6% of patients had an estimated glomerular function <60 mL/min.[22] In the Longitudinal Investigation of Thromboembolism Etiology study, during the mean follow-up time of 11.8 years, the adjusted relative risk (RR) of venous thromboembolism was significantly higher in patients with mild renal impairment (RR, 1.28; 95% confidence interval [CI], 1.02-1.59) and in patients with stage 3/4 chronic kidney disease (RR, 2.09; 95% CI, 1.47-2.96) compared with patients with normal renal function.[23] In the Longitudinal Investigation of Thromboembolism Etiology study, the risk of venous thromboembolism in patients with serum creatinine levels ≥1.5 mg/dL was almost double the risk in patients with serum creatinine levels <1.10 mg/dL (RR, 1.86; 95% CI, 1.21-2.81).[23] The association between renal function and venous thromboembolism has been found across multiple ethnicities.[17]

Renal insufficiency is associated with worse clinical outcomes and more serious comorbid conditions including congestive heart failure, hypertension, and diabetes in patients with venous thromboembolism.[19,24-26] In the Worcester Venous Thromboembolism Study, patients with venous thromboembolism and estimated glomerular function <30 mL/min/1.73 m^2 had a higher risk of recurrent venous thromboembolism (hazard ratio [HR], 1.83; 95% CI, 1.03-3.25), major bleeding episodes (HR, 2.30; 95% CI, 1.28-4.16), and all-cause mortality (HR, 1.70; 95% CI, 1.12-2.57) during a 3-year follow-up compared with patients with venous thromboembolism and estimated glomerular rate ≥90 mL/min/1.73 m^2.[24] In the Registro Informatizado de Enfermedad TromboEmbólica, a prospective registry study of consecutive patients with acute venous thromboembolism, patients with a creatinine clearance <30 mL/min had an increased incidence of fatal bleeding, fatal pulmonary embolism, and overall death compared with patients with a creatinine clearance >30 mL/min.[25,26] However, the relative risk of fatal pulmonary embolism and fatal bleeding differed by type of venous thromboembolism. Patients with a creatinine clearance <30 mL/min presenting with overt pulmonary embolism were at an increased risk of fatal pulmonary embolism compared with patients with normal renal function, whereas patients with a creatinine clearance <30 mL/min presenting with deep vein thrombosis were at an elevated risk of fatal bleeding.[25]

DIRECT ORAL ANTICOAGULANTS IN PATIENTS WITH RENAL IMPAIRMENT AND VENOUS THROMBOEMBOLISM

Glomerular filtration rate is not usually directly measured in routine clinical practice. Instead, there are various equations that use serum creatinine to measure creatinine clearance or glomerular filtration rate and that take into account factors including ethnicity and weight. The Modification of Diet in Renal Disease equation and the Chronic Kidney Disease Epidemiology Collaboration equations estimate glomerular filtration rate in mL/min per 1.73 m^2 and incorporate ethnicity into the equations.[27,28] The Cockcroft–Gault equation estimates creatinine clearance in mL/min, taking body weight into account.[29] Patients may be in different renal impairment stratification categories according to the equation used. The direct oral anticoagulant phase 3 trials all estimated renal function with Cockcroft–Gault using actual body weight and excluded patients with calculated creatinine clearance of ≤30 mL/min for dabigatran, <30 mL/min for edoxaban and rivaroxaban, and serum creatinine >2.5 mg/dL or a calculated creatinine clearance of <25 mL/min for apixaban.[30-35]

Direct oral anticoagulants have renal excretion rates ranging from 27% to 80% of the absorbed doses (dabigatran, 80%;