stated in the "Discussion" section of our article, it is unlikely that the herpes zoster experienced by these patients was caused by the vaccine virus strain. In this regard, we agree with Dr Bubb that vaccination is unlikely to be the cause of the increased risk of zoster during the 42 days postvaccination in the current immunosuppressant users. However, there are several potential explanations for our findings: (1) administration of the vaccine could possibly trigger herpes zoster in response to the antigen load in some immunosuppressed patients, (2) current immunosuppressant use could delay the immune response to the zoster vaccine, leading to a higher risk of herpes zoster in a population already at risk (ie, as an indicator of immune response, peak antibody levels after zoster vaccination in elderly individuals without immune-mediated diseases is 21 days[10] but is likely longer in patients receiving immunosuppressants), (3) current immunosuppressant use by itself could increase the risk of herpes zoster, and (4) current use of immunosuppressants could indicate a population that is fundamentally different from remote users in ways that are not captured using an observational design.

In conclusion, we agree that patients with certain immune-mediated diseases are at a higher risk of herpes zoster, and therefore, measures should be undertaken to maximize immunization of these individuals with the zoster vaccine in a safe and effective manner.

**T. Craig Cheetham, PharmD, MS**
**Lina S. Sy, MPH**
**Steven J. Jacobsen, MD, PhD**
Kaiser Permanente
Pasadena, CA

1. Cheetham TC, Marcy SM, Tseng H-F, et al. Risk of herpes zoster and disseminated varicella zoster in patients taking immunosuppressant drugs at the time of zoster vaccination. *Mayo Clin Proc*. 2015; 90(7):865-873.
2. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host [published correction appears in *Clin Infect Dis*. 2014;59(1):144] *Clin Infect Dis*. 2014;58(3):309-318.
3. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008; 57(RR-5):1-30.
4. Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction [published correction appears in *Mayo Clin Proc*. 2008;83(2):255] *Mayo Clin Proc*. 2007;82(11):1341-1349.
5. Smitten AL, Choi HK, Hochberg MC, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. *Arthritis Rheum*. 2007;57(8):1431-1438.
6. Wolfe F, Michaud K, Chakravarty EF. Rates and predictors of herpes zoster in patients with rheumatoid arthritis and non-inflammatory musculoskeletal disorders. *Rheumatology (Oxford)*. 2006;45(11): 1370-1375.
7. Gupta G, Lautenbach E, Lewis JD. Incidence and risk factors for herpes zoster among patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2006;4(12):1483-1490.
8. Borba EF, Ribeiro AC, Martin P, Costa LP, Guedes LK, Bonfá E. Incidence, risk factors, and outcome of Herpes zoster in systemic lupus erythematosus. *J Clin Rheumatol*. 2010;16(3): 119-122.
9. Chakravarty EF, Michaud K, Katz R, Wolfe F. Increased incidence of herpes zoster among patients with systemic lupus erythematosus. *Lupus*. 2013;22(3):238-244.
10. Weinberg A, Zhang JH, Oxman MN, et al; US Department of Veterans Affairs (VA) Cooperative Studies Program Shingles Prevention Study Investigators. Varicella-zoster virus-specific immune responses to herpes zoster in elderly participants in a trial of a clinically effective zoster vaccine. *J Infect Dis*. 2009;200(7):1068-1077.

http://dx.doi.org/10.1016/j.mayocp.2015.09.002

## New Oral Anticoagulants in Elderly Adults With Chronic Kidney Disease

***To the Editor:*** I read with interest the review article by Ponticelli et al[1] on drug management in the elderly adult with chronic kidney disease (CKD) that was published in the May 2015 issue of *Mayo Clinic Proceedings* and agree with their recommendations. Of note, the section on oral anticoagulants does not include or comment on the 4 new oral anticoagulants (NOAs) that have been approved by the US Food and Drug Administration (FDA) over the past 5 years. The NOAs approved are dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), and, recently, edoxaban (Savaysa).[2,3]

Atrial fibrillation (AF) is a common disorder in elderly adults. About 12% of AF cases occur in adults 75 to 84 years of age, and more than 33% of patients with AF are 80 years or older. Atrial fibrillation has a global prevalence of about 33.5 million cases and an incidence of approximately 5 million new cases per year. Atrial fibrillation is associated with a 5-fold increased risk of stroke. In the United States, AF accounts for more than 467,000 hospital admissions and more than 99,000 deaths per year.[4] Recently, the NOAs have been gradually replacing warfarin, a vitamin K antagonist that was the standard of care for about 60 years. Thus, I offer a few additional comments for the primary care physician, including the need for renal risk stratification when using the NOAs.[2,3]

Typically, the vitamin K antagonist drugs are used for AF in patients with prosthetic heart valves, mitral valve stenosis, severe valvular disease, or severe renal dysfunction, whereas the NOAs are mostly indicated for nonvalvular AF. The field of NOA is evolving, and new indications, boxed warnings, and precautions have been added since their initial approval by the FDA.[3,5-8]

The first NOA approved in the United States was dabigatran, and its approval was based mostly on the RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial that randomized participants to either warfarin or 1 of 2 doses of dabigatran (110 mg or 150 mg twice daily).[9] The FDA did not approve the 110-mg dose. The FDA approved the dose of 150 mg twice daily in all patients, including patients with a creatinine

**TABLE. Dosing of New Oral Anticoagulants Based on Stage of Chronic Kidney Disease[a]**

| Stages of chronic kidney disease (CKD) | Estimated glomerular filtration rate (eGFR) | Description | Dabigatran (Pradaxa) dose for NVAF and DVT/PE[b] | Rivaroxaban (Xarelto) dose for NVAF, DVT/PE[c]/stroke prophylaxis | Apixaban (Eliquis) dose for NVAF, DVT/PE,[d] and reduction of embolism/stroke treatment | Edoxaban (Savaysa) dose for NVAF and DVT/PE treatment |
|---|---|---|---|---|---|---|
| CKD1 | >90 mL/min per 1.73 $m^2$ | Renal injury without decreased eGFR | 150 mg twice daily | 20 mg daily;<br>HR: 10 mg daily<br>KR: 10 mg daily | 5 mg bid;<br>HR: 2.5 mg bid<br>KR: 2.5 mg bid | eGFR >95: avoid<br>eGFR 90-95:<br>60 mg daily[e] |
| CKD2 | 60-89 mL/min per 1.73 $m^2$ | Mildly decreased eGFR | 150 mg twice daily | 20 mg daily;<br>HR: 10 mg daily<br>KR: 10 mg daily | 5 mg bid;<br>HR: 2.5 mg bid<br>KR: 2.5 mg bid | 60 mg daily[e] |
| CKD3 | 30-59 mL/min per 1.73 $m^2$ | Moderately decreased eGFR | 150 mg twice daily | 15 mg daily;<br>HR: 10 mg daily<br>KR: 10 mg daily | 2.5 mg bid;<br>HR: 2.5 mg bid<br>KR: 2.5 mg bid | 60 mg daily,[e]<br>30 mg daily if used with P-gp inducers |
| CKD4 | 15-29 mL/min per 1.73 $m^2$ | Severely decreased eGFR | 75 mg twice daily | 15 mg daily;<br>HR: 10 mg daily<br>KR: 10 mg daily | 2.5 mg bid;<br>HR: 2.5 mg bid<br>KR: 2.5 mg bid | 30 mg daily |
| CKD5 | <15 mL/min per 1.73 $m^2$ | Renal failure | Avoid | Avoid | Avoid;<br>HD: 2.5-5 mg bid | Avoid |

[a]bid = twice a day; DVT = deep venous thrombosis; HD = hemodialysis; HR = prophylaxis of DVT following hip replacement; KR = prophylaxis of DVT following knee replacement; NVAF = nonvalvular atrial fibrillation; PE= pulmonary embolism; P-gp = permeability glycoprotein; Rx = treatment.

[b]Dabigatran dose for DVT and PE Rx following 5-10 days of initial Rx with parenteral anticoagulant. It is also approved for RRR (reduction in the risk of recurrence) of DVT and PE for CKD1-3 but not dose provided for CKD4 -5.

[c]Xarelto for the Rx of DVT, PE, and RRR dose is 15 mg bid for first 21 days. Thereafter, 20 mg daily.

[d]Eliquis for Rx of DVT and PE: 10 mg bid for 7 days, followed by 5 mg bid. For RRR DVT and PE following initial Rx is 2.5 mg bid.

[e]Savaysa dose for DVT and PE: following 5-10 days of initial Rx with parenteral anticoagulant.

Data from *Cleve Clin J Med*,[2] *El Paso Physician*,[3] and prescribing information for Pradaxa, Xarelto, Eliquis, and Savaysa. From *El Paso Physician*,[3] with permission.

clearance of 15 to 30 mL/min per 1.73 $m^2$ (to convert values to mL/s per $m^2$, multiply by 0.0167).[10-13] This range corresponds to an estimated glomerular filtration rate (eGFR) of 15 to 29 mL/min per 1.73 $m^2$ or a diagnosis of CKD stage 4 (CKD4). This dosing scheme is in stark contrast to doses used in more than 70 countries worldwide, where the 150-mg dose is contraindicated in CKD4.[13] As in most drug trials, patients with CKD4 were excluded in the RE-LY trial.[9,12,13] Not surprisingly, 3781 serious adverse effects were noted in the 2011 US postmarketing experience with dabigatran. These events included death (452 cases), hemorrhage (2367 cases), acute renal failure (291 cases), stroke (644 cases), and suspected liver failure (15 cases).[12] Thirteen months after dabigatran initial approval in the United States, the manufacturer changed the dose and product guidelines. The new dosage is 75 mg twice daily for patients with a creatinine clearance of 15 to 30 mL/min per 1.73 $m^2$ or CKD4.[11-13]

To avoid some of the clinical problems noted with dabigatran, a simple renal risk stratification guideline was proposed that includes the determination of the eGFR that uses serum creatinine for the Modification of Diet in Renal Disease (MDRD) formula and CKD stage.[2] The MDRD formula is used by most US laboratories and includes 4 variables: serum creatinine level, age, sex, and race. The MDRD formula is more accurate than the Cockcroft-Gault equation (CGe) described 39 years ago,[14] which was used in the RE-LY trial. The CGe was developed before the availability of standardized creatinine assays, and it is estimated that its use results in a 10% to 40% overestimate of creatinine clearance.[15] Indirect support for using a renal risk stratification comes from a recent study by Reilly et al.[16] They reported that renal function was the most important determinant of dabigatran concentration, and age is the most important covariate.[16]

Most US laboratories now provide an eGFR and the stage of CKD.[2,3] Thus, if dabigatran is used, one should follow current manufactures' dosing guidelines for patients with CKD stages 1 through 3, ie, 150 mg twice daily. If CKD4 is detected, the updated recommended dosage is 75 mg twice daily. If the patient has stage 5 CKD (eGFR, <15 mL/min per 1.73 $m^2$), dabigatran

is not indicated (Table). Similar steps can be followed for the other NOAs, and we need to adhere to their respective guidelines.[2,3]

If NOAs are to be used in patients with nonvalvular AF, the $CHA_2DS_2$-VASc score (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65-75 years, sex category [female]) should be determined. This score gives special attention to congestive heart failure, hypertension, age 75 years and older, diabetes, women, and history of stroke, transient ischemic attack, or systemic embolism.[2,3] A score of 2 is assigned to patients who have a stroke or are 75 years or older. A score of 1 is assigned to each of the remaining risk factors, if present. A total score of 0 requires no treatment, and a score of 2 or more requires treatment. For patients with a score of 1, treatment is decided on an individual basis. Moreover, a renal risk stratification should be done for all NOAs using a comprehensive metabolic panel before treatment begins and 1 week after initiation of the NOA or if there is a change in the patient's clinical condition.[2,3] It should be noted that the suggested dosing of the NOAs based on CKD stages has not been validated for clinical use. However, the actual dosing is the same for equivalent stages of renal dysfunction based on CGe and the current NOA prescribing information.[5-8] The guideline highlights the need for CKD staging to prevent adverse effects.[2,3]

As we accumulate more experience with the NOAs, we will have a better understanding of the proper selection of each of these agents. The net clinical benefit[17] obtained should be evaluated with each agent in this upcoming era of individualized patient care and precision medicine. The NOAs can be a welcome addition to our armamentarium to treat patients who need anticoagulation. Because of the narrow therapeutic indices of the NOAs,[18] use of the proposed renal risk stratification is suggested to avoid some of the risks, morbidity, mortality, and expense in managing serious NOA adverse effects.[2,3,11-13]

**Patricio Pazmiño, MD, PhD**
Nephrology, Internal Medicine & Hypertension Center
El Paso, TX

1. Ponticelli C, Sala G, Glassock RJ. Drug management in the elderly adult with chronic kidney disease: a review for the primary care physician. *Mayo Clin Proc*. 2015;90(5):633-645.
2. Pazmiño P. Renal risk stratification with the new oral anticoagulants [letter] *Cleve Clin J Med*. 2013; 80(11):733-734.
3. Pazmiño P. The need for renal risk stratification when using the new oral anticoagulants. *El Paso Physician*. 2015;38(2):7-9.
4. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64(21):e1-e76.
5. *Pradaxa [package insert]*. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; March 2011 and April 2013.
6. *Xarelto [package insert]*. Titusville, NJ: Janssen Pharmaceuticals, Inc; March 2013.
7. *Eliquis [package insert]*. Princeton, NJ: Bristol-Myers Squibb Company; December 2012.
8. *Savaysa [package insert]*. Parsippany, NJ: Daiichi Sankyo Company, Limited; April 2015.
9. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation [published correction appears in *N Engl J Med*. 2010;363(19):1877] *N Engl J Med*. 2009; 361(12):1139-1151.
10. Kowey PR, Naccarelli GV. The Food and Drug Administration decision not to approve the 110 mg dose of dabigatran: give us a way out [editorial] *Am J Med*. 2012;125(8):732.
11. Pazmiño PA. Dabigatran: a nephrological way out [letter] *Am J Med*. 2013;126(4):e21.
12. Pazmiño PA. Dabigatran side effects: nephrological perspective and opinion. [letter]. Comments in Dabigatran: Uncharted Waters and Potential Harms. *Ann Intern Med*. 2012;157(1): 66-68.
13. Pazmiño PA. Dabigatran associated acute renal failure (DAARF). *El Paso Physician*. 2011;34(6):7-9.
14. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. *JAMA*. 2015; 313(8):837-846.
15. Inker LA, Perrone RD. Assessment of kidney function. UpToDate website. http://www.uptodate.com/contents/assessment-of-kidney-function?source=search_result&search=Assessment+of+kidney+function&selectedTitle=1~150. Accessed June 24, 2015.
16. Reilly PA, Lehr T, Haertter S, et al; RE-LY Investigators. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J Am Coll Cardiol*. 2014;63(4):321-328.
17. Banerjee A, Lane DA, Torp-Pedersen C, Lip GY. Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a 'real world' atrial fibrillation population: a modelling analysis based on a nationwide cohort study. *Thromb Haemost*. 2012;107(3): 584-589.
18. Powell RJ. Are new oral anticoagulant dosing recommendations optimal for all patients? *JAMA*. 2015;313(10):1013-1014.

http://dx.doi.org/10.1016/j.mayocp.2015.09.004

## In reply—New Oral Anticoagulants in Elderly Adults With Chronic Kidney Disease

We thank Dr Pazmiño for his comments on our article. Many of the new oral anticoagulants (NOAs) are excreted to a substantial extent by the kidney, and it is certainly necessary to consider dosage adjustments on the basis of the patient's estimated glomerular filtration rate. It is true that the occurrence of nonvalvular atrial fibrillation is increased in patients with advanced kidney failure, and use of NOAs has some appeal for this condition compared with other oral anticoagulants such as vitamin K antagonists (warfarin). However, we recommend great caution with the use of NOAs in patients with advanced renal failure because it can be extremely difficult to assess the appropriate safe and effective dosing regimen in these patients, and if serious bleeding occurs