REPLY: Apixaban Dosing in Chronic Kidney Disease

Differences Between U.S. and E.U. Labeling

We thank Dr. Brophy for his kind comments on our recent paper (1). He highlights a relevant issue for the use of apixaban in patients with atrial fibrillation (AF) with severe chronic kidney disease (CKD). Indeed, current European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) indications differ considerably (2,3).

In the EMA summary of product characteristics, for patients with severe CKD (i.e., creatinine clearance rate of 15 ml/min to 29 ml/min according to Cockroft-Gault equation), apixaban plasma concentrations were reported as increased up to 44% compared to subjects with normal renal function (i.e., creatinine clearance rate >80 ml/min) (2) when the 5-mg twice-daily dose is administered. Based on this consideration, EMA recommended use of the lower apixaban dose (i.e., 2.5 mg twice daily) irrespective of other criteria for dose reduction to avoid a higher bleeding risk (3). EMA recommendations have been also acknowledged and implemented by the European Heart Rhythm Association practical guide on use of non-vitamin K antagonist oral anticoagulants (NOACs) (4).

Even if the FDA reported similar pharmacokinetic data, their recommendation was still to use apixaban 2.5 mg twice daily only when the patient qualifies for 2 of the 3 criteria used in the main phase III study (age ≥80 years, weight ≤60 kg and serum creatinine level ≥1.5 mg/dl), irrespective of creatinine clearance (3), notwithstanding the fact that the phase III trial excluded patients with a Cockcroft-Gault creatinine clearance rate <25 ml/min.

Interestingly, the FDA recommended use of apixaban 5 mg twice daily (and without any further dose adjustment) in AF patients with end-stage renal disease undergoing hemodialysis. Indeed, systemic exposure to apixaban 5 mg twice daily followed by a dialysis procedure was 17% higher compared to patients with normal renal function (5). In contrast, the EMA label did not support the use of apixaban in AF patients with end-stage renal disease.

As Dr. Brophy suggests, we believe that these data should be known by all physicians when making decisions on which NOACs to prescribe in patients with different degrees of renal disease. Given the high risk of patients with CKD in terms of thromboembolic and bleeding risks, caution is needed when NOACs are used in these patients.

Marco Proietti, MD
***Gregory Y.H. Lip, MD**

*University of Birmingham Institute of
Cardiovascular Sciences
City Hospital
Dudley Road
B18 7QH, Birmingham, United Kingdom
E-mail: g.y.h.lip@bham.ac.uk

http://dx.doi.org/10.1016/j.jacc.2016.11.075

Please note: Dr. Proietti has received a small consulting fee from Boehringer Ingelheim. Dr. Lip is a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo; and a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo.

REFERENCES

1. Lau YC, Proietti M, Guiducci E, Blann AD, Lip GYH. Atrial fibrillation and thromboembolism in patients with chronic kidney disease. J Am Coll Cardiol 2016;68:1452–64.

2. Eliquis [Summary of Product Characteristics]. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf. Accessed November 9, 2016.

3. Eliquis [Medical Review]. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155Orig1s000MedR.pdf. Accessed November 9, 2016.

4. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonists anticoagulants in patients with non-valvular atrial fibrillation. Europace 2015;17:1467–507.

5. Eliquis [Product Label]. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202155s012lbl.pdf. Accessed November 9, 2016.