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Response to "Critical Analysis of Apixaban Dose Adjustment Criteria"

Stephen R. Mandt[1,*], Puneet Gaitonde[2,*], Antoinette Ajavon-Hartmann[1,*], Christian Klem[1], Anthony Chan[2], and Arnaud Bastien[1]

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Dear Editor,

We would like to thank Dr. Vu and colleagues for their literature-based review of apixaban dose-adjustment criteria (DAC) for the reduction of risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF) and treatment of venous thromboembolism (VTE).[1] Dr. Vu and colleagues explored each apixaban DAC and its effect on pharmacokinetics and have questioned: (1) Applicability of DAC in NVAF and not in VTE, (2) How the DAC was chosen, and (3) If the DAC should be re-evaluated. We acknowledge the questions and are providing the Sponsor's perspective with rationale and scientific context.[1]

There is no Health Authority requirement that all approved indications for a medication have identical dosage and administration criteria. Dosing for each indication is geared toward providing the optimal benefit-to-risk profile for a specific diagnosis and patient population. Apixaban was approved in 2012 by the United States Food and Drug Administration (FDA) for reducing risk of stroke and systemic embolism in patients with NVAF. Apixaban was approved by the FDA for treatment of VTE and reduction in risk of VTE recurrence in 2014. Overall, apixaban has been approved in >100 countries worldwide for these indications. To date, there have been no regulatory requests to revise the DAC.

In patients at risk for stroke associated with NVAF requiring anticoagulation, a failure of efficacy could result in substantial morbidity and mortality. In reviewing data from both pharmacokinetic analyzes in phase 1 and clinical outcomes in phase 2 trials, 5 mg twice daily dosing (BID) appeared to have efficacy without a proportional increase in bleeding.[2–4] Apixaban dosages greater than 5 mg BID showed potential for greater efficacy, but also had a higher risk of bleeding. Therefore, apixaban 5 mg BID was selected to balance efficacy and safety for most patients for the NVAF indication.

Furthermore, during review of both pharmacokinetic studies and clinical outcomes from phase 2 trials, certain groups of NVAF patients demonstrated a lower total clearance of apixaban and an associated higher risk of bleeding. For this reason, the phase 3 ARISTOTLE Trial tested a reduced apixaban dose of 2.5 mg BID for patients who met at least two of the following three criteria: (1) Age ≥80 years, (2) Body weight ≤60 kg, or (3) Serum creatinine ≥1.5 mg/dL. It is important to note that meeting only one of the criteria was not sufficient basis to decrease the dose. Dr Vu et al. have cited in their article this secondary analysis from ARISTOTLE supporting the DAC strategy. The secondary analysis by Alexander et al. demonstrated that the dose-reduction criteria used in the ARISTOTLE trial were chosen because, in combination, they predict increased apixaban exposure. The same criteria are also predictive of bleeding risk.[5] We direct the reader to Figure 1 and Table 3 from this secondary analysis, which demonstrate preserved efficacy and safety utilizing the approved DAC for apixaban.

The approved dosage for apixaban for VTE treatment, which is 10 mg BID for seven days, followed by 5 mg BID, was also supported by the totality of evidence from the phase 2 deep vein thrombosis study and a dose-response model.[3] It is worth noting that patients with acute VTE are at increased risk of clot extension or embolism and have elevated Factor Xa levels. Thus, a higher initial Factor Xa inhibiting dose was included within the treatment regimen to bring the Factor Xa inhibition to the same level as that observed in patients treated with low molecular weight heparin (LMWH). This was the rationale for selecting the 10 mg BID dose. This higher dose was given for seven days due to evidence

[1] Bristol Myers Squibb, Inc., Lawrence Township, NJ, USA
[2] Pfizer, Inc., New York, NY, USA

*Equal contributor

Corresponding Author:
Antoinette Ajavon-Hartmann, Bristol Myers Squibb, Inc., 3401 Princeton Pike, Lawrence Township, NJ 08648, USA.
Email: antoinette.ajavon-hartmann@bms.com

from a meta-analysis showing the highest risk for VTE recurrence during the first week after an index VTE diagnosis.[6] The decision not to adjust the apixaban dose using the criteria for NVAF patients is due to the clinical importance of not underdosing patients with active clots who may be at higher risk of recurrent VTE.[3]

Regarding NVAF patients with end stage renal disease, more clinical data is forthcoming which may provide further clarity on the optimal dose for apixaban in specific patient population. We eagerly await the peer reviewed publication of the REnal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillatio (RENAL-AF) (NCT02942407) trial results and the finalization and publication of the AXADIA (NCT02933697) clinical trial to add clinical trial outcome information to the body of evidence supporting the use of apixaban in this subpopulation of patients with NVAF. The preliminary results for RENAL-AF have been presented and are currently publicly available. The AXADIA trial is currently still ongoing. The FDA approved dose of apixaban 5 mg BID in the population of patients with end stage renal disease requiring dialysis is based on pharmacokinetic and pharmacodynamic data submitted by the Sponsor and informed the DAC in patients with NVAF.

It should be emphasized that a careful analysis of the totality of scientific evidence from all stages of apixaban's development informed the optimal dose for each indication. The FDA Approval Package (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155Orig1s000TOC.cfm) provides in-depth analysis of all data.

With the positive clinical outcomes and benefit-to-risk profile of apixaban at currently approved doses, we see no need to re-evaluate the apixaban DAC. Even though the ultimate test of a dose for any medication is in a randomized controlled trial (RCT) setting, multiple real world data studies, both sponsored and independent, have demonstrated broadly consistent effectiveness and safety in a wide variety of eligible patient populations.[7]

Declaration of Conflicting Interests

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ORCID iD

Antoinette Ajavon-Hartmann https://orcid.org/0000-0003-0690-5989

References

1. Vu A, Qu TT, Ryu R, Nandkeolyar S, Jacobson A, Hong LT. Clinical and Applied Thrombosis/Hemostasis 2021; 27 https://doi.org/10.1177/10760296211021158
2. Zeitouni M, Giczewska A, Lopes RD, et al. Clinical and pharmacological effects of Apixaban dose adjustment in the ARISTOTLE trial. *J Am Coll Cardiol*. 2020;75(10):1145–1155. https://doi.org/10.1016/j.jacc.2019.12.060
3. Buller H, Deitchman D, Prins M, et al. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. *J Thromb Haemostasis*. 2008;6(8):1313–1318. https://doi.org/10.1111/j.1538-7836.2008.03054.x
4. Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. *J Thromb Haemost*. 2007;5(12):2368–2375. https://doi.org/10.1111/j.1538-7836.2007.02764.x
5. Alexander JH, Andersson U, Lopes RD, et al. Apixaban 5 mg twice daily and clinical outcomes in patients with atrial fibrillation and advanced Age. *Low Body Weight, or High Creatinine: A Secondary Analysis of a Randomized Clinical Trial. JAMA Cardiol*. 2016;1(6):673–681. doi:10.1001/jamacardio.2016.1829
6. Limone BL, Hernandez AV, Michalak D, Bookhart BK, Coleman CI. Timing of recurrent venous thromboembolism early after the index event: a meta-analysis of randomized controlled trials. *Thromb Res*. 2013;132(4):420–426. https://doi.org/10.1016/j.thromres.2013.08.003
7. Lip GYH, Keshishian A, Li X, et al. Effectiveness and safety of oral anticoagulants Among nonvalvular atrial fibrillation patients: the ARISTOPHANES study. *Stroke*. 2018;49(12):2933–2944. https://doi.org/10.1161/STROKEAHA.118.020232