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LETTER TO THE EDITOR

# Inconsistencies in reporting of renal elimination among NOACs: the case of apixaban

Dear Sir, We would like to discuss an apparent lack of consistency in the reporting of renal elimination data for non-vitamin K antagonist oral anticoagulants (NOACs) and potential clinical consequences with special reference to apixaban.

Four NOACs are currently approved: dabigatran, rivaroxaban, apixaban, and edoxaban. For the principal clinical indications, non-valvular atrial fibrillation, and venous thromboembolism (VTE), all NOACs have demonstrated at least non-inferiority with respect to efficacy and adverse reaction profile compared with warfarin.[1,2] Choosing the most appropriate NOAC depends on individual patient factors, among which renal function is of particular clinical relevance, because patients with renal insufficiency have an increased risk of thrombosis and bleeding.[3,4]

When assessing the safety profile of NOACs in patients with impaired renal function, knowledge of renal clearance is crucial. However, as the renal clearance can be reported as the percentage excreted through the kidneys of either (a) intravenously *administered* drug or (b) *absorbed* drug after oral intake, differences may occur when reporting this measure. Currently, there is no specific guidance from regulatory authorities on how renal clearance should be reported, as part of either total clearance, apparent oral clearance, or absolute clearance.[5,6] Consequently, the reporting of renal elimination of NOACs is inconsistent and non-transparent (Table 1).

To illustrate the issue, consider apixaban, which is approved for use in patients with creatinine clearance (CrCl) $\geq$15 mL/min[7,8]. The Summary of Product Characteristics (SmPC) states that "*renal excretion of apixaban is about 27% of total clearance*."[7,8] This likely reflects the results from intravenous phase I trials presented as conference abstracts in 2008 and 2009, but without subsequent peer-review and publication.[9,10] However, in the scientific literature, renal clearance of apixaban is usually referenced from a peer-reviewed mass balance study by the marketing authorization holder, stating that 22–24% of the *orally* ingested apixaban dose was recovered unchanged in the urine.[11] Because bioavailability is about 50%, use of this reference to assess the renal contribution to elimination of systemically available apixaban may result in erroneously high estimates (44–48%). Overall, we do not believe the available data fully clarify the extent of renal elimination of apixaban after oral administration.

Exploring the clinical pharmacology of apixaban in renally impaired patients further, the SmPC states that the area under the plasma concentration–time curve (AUC) is increased by 29% and 44% in patients with moderate (CrCl 30–50 mL/min) and severe (CrCl 15–29 mL/min) renal impairment, respectively[7,8]. These data are, however, based on single-dose studies in very few patients ($N = 7 + 7$), with high inter-individual variability in AUC Measurements[12]. During continuous treatment with apixaban 5 mg twice daily in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial Aristotle, patients with moderate renal impairment demonstrated an even higher AUC increase (38%).[12]

Although treatment with apixaban was associated with a lower risk of major bleeding compared with warfarin in clinical trials,[1,2,13] patients with impaired renal function had the highest rates of major bleedings on apixaban, despite only moderate AUC increases in pharmacokinetic studies. In the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy trial "(AMPLIFY)", patients in the apixaban arm with CrCl $\leq$ 50 mL/min had a hazard ratio of major bleeding of 6.5 (95%CI 2.2–19) compared with patients with CrCl $>$ 50 mL/min (rates for major bleeding: 2.9% [5/175] vs. 0.4% [10/2270]).[3] Similarly, major bleeding rates in the treatment arm receiving 5mg apixaban twice daily in the Apixaban after the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy — Extended treatment trial "(AMPLIFY-EXT)" were 14.0% (6/43) in

Table 1. Reporting of renal clearances for non-vitamin K antagonist oral anticoagulants

| | Specific statement of renal clearances (referred route of administration, if specified) | |
|---|---|---|
| | EMA SmPC[a] | FDA label[b] |
| Dabigatran | "The dabigatran-derived radioactivity was eliminated primarily in the urine (85%)." (intravenous) | "Renal clearance of dabigatran is 80% of total clearance." (intravenous)<br>"7% of radioactivity is recovered in urine." (oral) |
| Rivaroxaban | "1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine." (not specified) | "one-third of the absorbed dose is excreted in the urine." (oral) |
| Apixaban | "Renal excretion accounts for about 27% of total clearance." (not specified) | "Renal excretion accounts for about 27% of total clearance." (not specified) |
| Edoxaban | | "Renal clearance accounts for approximately 50% of the total clearance." (not specified) |

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; SmPC, Summary of Product Characteristics;
[a]Available from: http://www.ema.europa.eu/ema/ [accessed 2015 April 30]
[b]Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm [accessed 2015 April 30]

patients with creatinine clearance ≤50 mL/min (5/175) compared with 3.9% (29/747) in patients with CrCl >50 mL/min.[13]

Non-inferiority in efficacy and safety of apixaban compared with warfarin was preserved in patients with mild and moderate renal impairment in phase III trials[14]. In severe renal impairment, data are less certain because patients with CrCl <25 mL/min were excluded from trials.[14] Until recently, halving of apixaban dose has been recommended in the majority of patients with severe renal impairment. Importantly, in 2014, apixaban was approved for treatment and prevention of VTE, for which full dose is recommended for all patients[7,8]. Apixaban is now being marketed as an attractive alternative to warfarin in the treatment of VTE, specifically declaring "*no dose adjustments required in patients with renal impairment*," although dose reduction is still recommended when used for non-valvular atrial fibrillation.[7,8] This recent and seemingly inconsistent change in dosing in patients with renal impairment appears to be based on very little clinical evidence, and the aforementioned single-dose pharmacokinetic study reporting surrogate measures in seven patients. In our opinion, available data are insufficient to substantiate such clinical recommendations.

In conclusion, we believe that more clinical data on the safety of apixaban in patients with severe renal impairment are warranted. For now, we encourage caution when treating patients with severely impaired renal function with apixaban or other NOACS. Finally, we encourage regulators to revise existing guidelines to explicitly define the reporting of renal clearance in the SmPCs in order to ensure consistency, transparency, and comparability among drugs, including NOACs.

## CONFLICT OF INTEREST

M. H., P. D., A. P., and T. G. declare no conflicts of interest.

E. L. G. has received speaker honoraria from AstraZeneca, Baxter, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer and has participated in advisory board meetings for AstraZeneca, Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb.

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