

# Industry Perspective

## Eliquis<sup>®</sup> (apixaban)

EMA Workshop: The role of PK and PD measurements in the use of  
DOACs

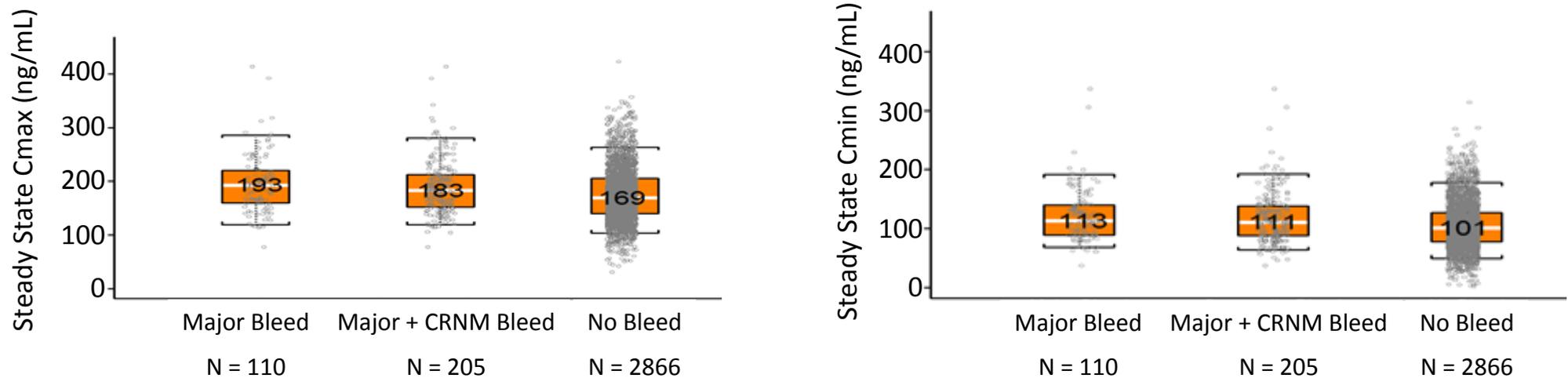
23 November 2015

# Apixaban and Therapeutic Drug Monitoring

- Pivotal studies of apixaban in each of its approved indications have demonstrated:
  - a favourable benefit-risk (BR) profile when used without TDM or TDM-based dose titration
  - superiority on efficacy and/or bleeding vs the standard of care
- A key question for this workshop is whether TDM could further improve the BR profile
- In order to consider approaches to answering this question, it is important to understand the existing evidence from clinical studies

# Monitoring of Apixaban Concentrations Does Not Enable Prediction of Bleeding Risk in Individual Patients

Population PK model predicted C<sub>max</sub> and C<sub>min</sub> for Subjects in ARISTOTLE with or without Bleeding Events

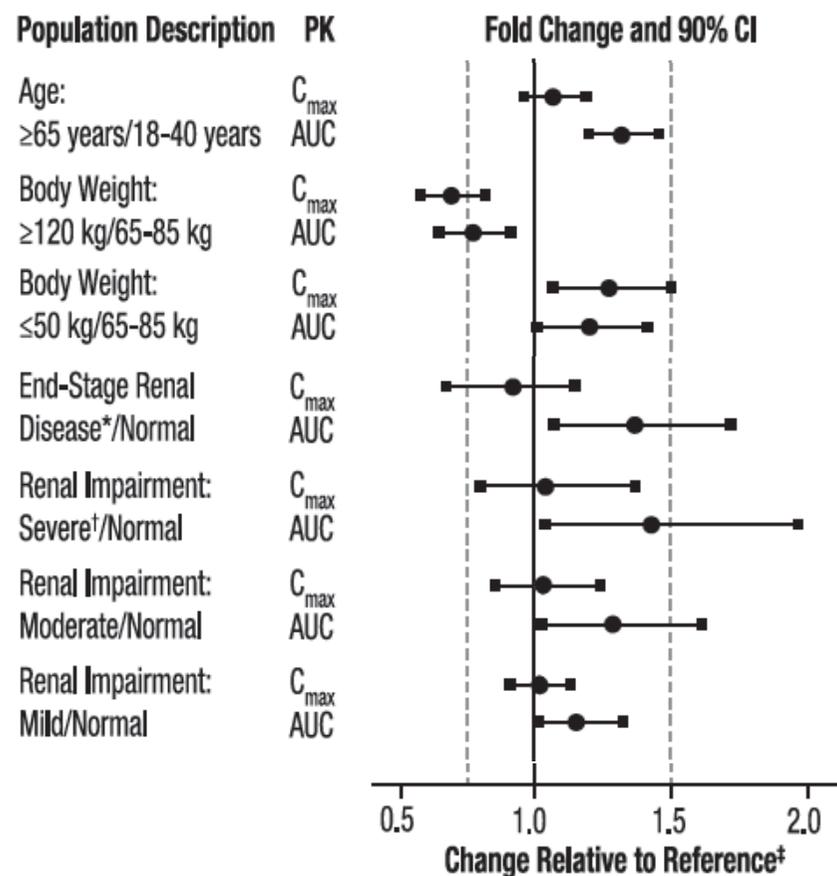


- There is extensive overlap in the range of apixaban exposures for patients who experienced bleeding events and for those who did not experience bleeding events
- Despite the extensive efficacy and safety database and Population PK modeling, it has not been possible to define a therapeutic range for apixaban

# Special Populations

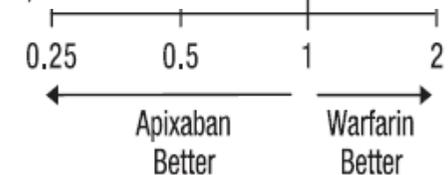
## Consistent Safety Results in Populations with Modest PK Effects

Effect of Specific Populations on PK of Apixaban



Major Bleeding by Subgroups in ARISTOTLE

Subgroup	No. of Patients	No. of Events (% per yr)		Hazard Ratio (95% CI)	P-value for Interaction
		Apixaban	Warfarin		
All Patients	18140	327 (2.13)	462 (3.09)	~0.7	0.64
Age					
<65 yrs old	5455	56 (1.2)	72 (1.5)	~0.7	
≥65 to <75 yrs old	7030	120 (2.0)	166 (2.8)	~0.7	
≥75 yrs old	5655	151 (3.3)	224 (5.2)	~0.7	
Weight					0.22
≤60 kg	1978	36 (2.3)	62 (4.3)	~0.5	
>60 kg	16102	290 (2.1)	398 (3.0)	~0.7	
Level of Renal Impairment					0.03
Severe or Moderate	3005	73 (3.2)	142 (6.4)	~0.5	
Mild	7565	157 (2.5)	199 (3.2)	~0.7	
Normal	7496	96 (1.5)	119 (1.8)	~0.7	



# Appropriateness of Measuring Anticoagulant PK or PD

## Routine TDM and dose titration

- Necessary for drugs with a narrow therapeutic window or high inter-individual variability in PK/PD
- Is not useful for individualized adjustment within a therapeutic range
- Attempts to adjust dosage for a target exposure level based on perceived risks may be detrimental rather than beneficial

## Measurement under special circumstances

- May be appropriate for any drug with dose-related safety concerns
  - Overdose
  - Special populations – patients atypical of those included in pivotal clinical trials
  - Urgent surgery or invasive procedure
  - Bleeding or other need for reversal agent or antidote

# Appropriate Measurement of Apixaban

- *“Although treatment with apixaban does not require routine monitoring of exposure, a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery.”* - Eliquis SmPC

Key question:

How do you interpret a laboratory test result, and how do you use the information to improve the benefit-risk for an individual patient?

# Guidance for Physicians in Exceptional Circumstances

Predicted Apixaban Steady-state Exposure (excerpted from SmPC Table 3)

	Apixaban Cmax (ng/mL)	Apixaban Cmin (ng/mL)
Median [5 <sup>th</sup> , 95 <sup>th</sup> Percentile]		
<i>Prevention of VTE: elective hip or knee replacement surgery</i>		
2.5 mg BID	77 [41, 146]	51 [23, 109]
<i>Prevention of stroke and systemic embolism: NVAF</i>		
2.5 mg BID*	123 [69, 221]	79 [34, 162]
5 mg BID	171 [91, 321]	103 [41, 230]
<i>Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE</i>		
2.5 mg BID	67 [30, 153]	32 [11, 90]
5 mg BID	132 [59, 302]	63 [22, 177]
10 mg BID	251 [111, 572]	120 [41, 335]

\* Dose adjusted population based on 2 or 3 dose reduction criteria in the ARISTOTLE study

The range of exposures from pivotal clinical studies of apixaban may be useful references to inform therapeutic decisions in special medical circumstances, such as overdose, emergency surgery, or suspicion of major deviations from tested exposures.

## Future Perspectives: How Do We Identify Situations Where Measurement May be Appropriate?

- It is important to understand the clinical conditions that influence benefit and risk, and not only apixaban exposure
- Ongoing safety surveillance including:
  - Additional pharmacovigilance: Targeted bleeding questionnaire to collect information on all reported cases of major bleeding
  - Enhanced pharmacovigilance: Active surveillance of databases to monitor hospitalisations for bleeding events and collect patients characteristics
- Evaluation of real world data to identify additional populations in whom the benefit-risk profile may differ from those in clinical trials
- Experience gained by the development of antidote and reversal agents

## Future Perspectives: What are the Ongoing or Planned Studies?

- Influence of comorbidities within approved indications
  - Atrial fibrillation patients with ACS
  - VTE treatment in patients with cancer
- Patient populations where safety, efficacy, and PK may be informative
  - Pediatrics – ongoing or planned studies of apixaban in 3 indications
  - Renal dialysis – plans to study patients with atrial fibrillation on dialysis
  - Bariatric surgery
  - Patients requiring reversal of anticoagulation

# Conclusions

- Apixaban has shown a favourable benefit-risk profile in each of the approved indications without a requirement for TDM or TDM-based dose titration.
- Studies have shown consistent efficacy and safety across high risk populations and overlap of exposures in patients with and without bleeding
- It should not be concluded that the benefit-risk profile would be improved using a strategy of TDM.
- Additional studies are underway or planned to further evaluate benefit and risk and the influence of both clinical conditions and exposure