Industry Perspective

Eliquis® (apixaban)

CSRC Thinktank: The role of PK and PD measurements in the use of NOACs

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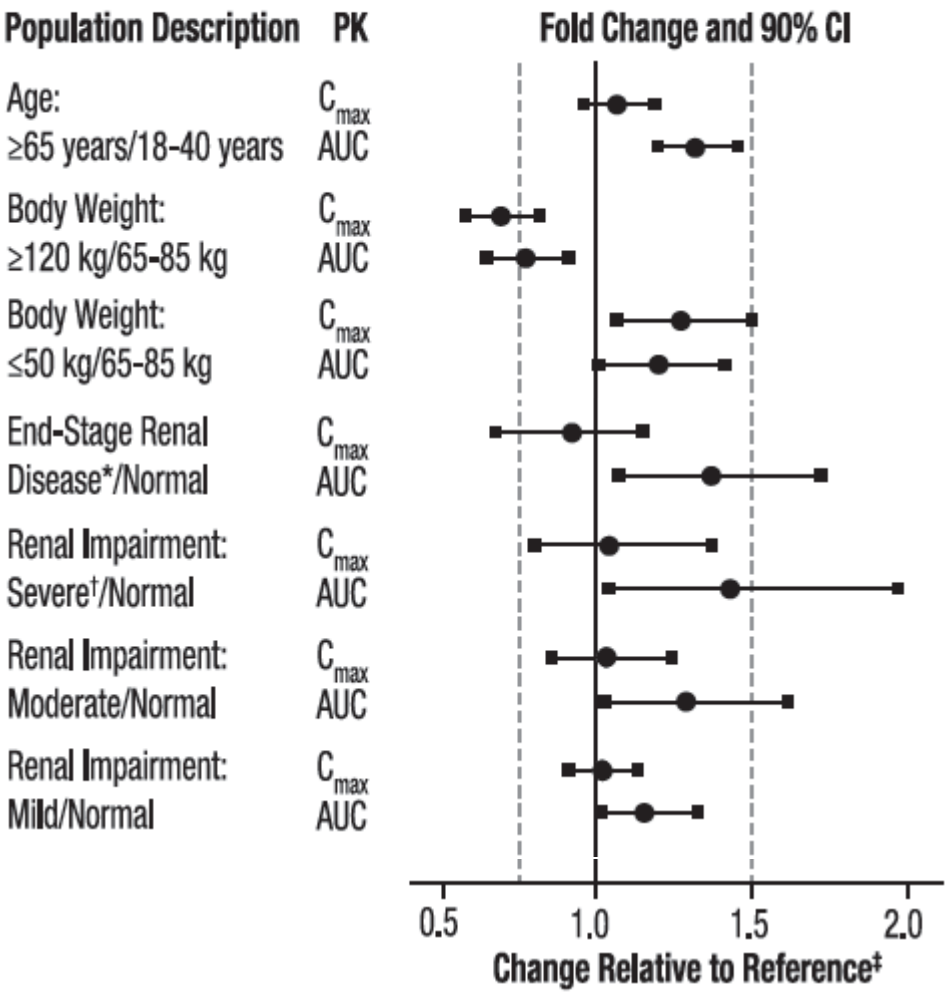
Apixaban and Therapeutic Drug Monitoring

- Pivotal studies of apixaban in each of its approved indications have demonstrated:
  - a favorable benefit-risk (BR) profile when used without TDM or TDM-based dose titration
  - superiority on efficacy and/or bleeding vs the standard of care
- Apixaban dosing in NVAF
  - 5 mg BID for most patients
  - 2.5 mg BID for patients with at least 2 out of 3 clinical criteria: (1) age ≥ 80, (2) body wt ≤ 60 kg, (3) creatinine ≥1.5 mg/dL
- A key question for this Thinktank 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

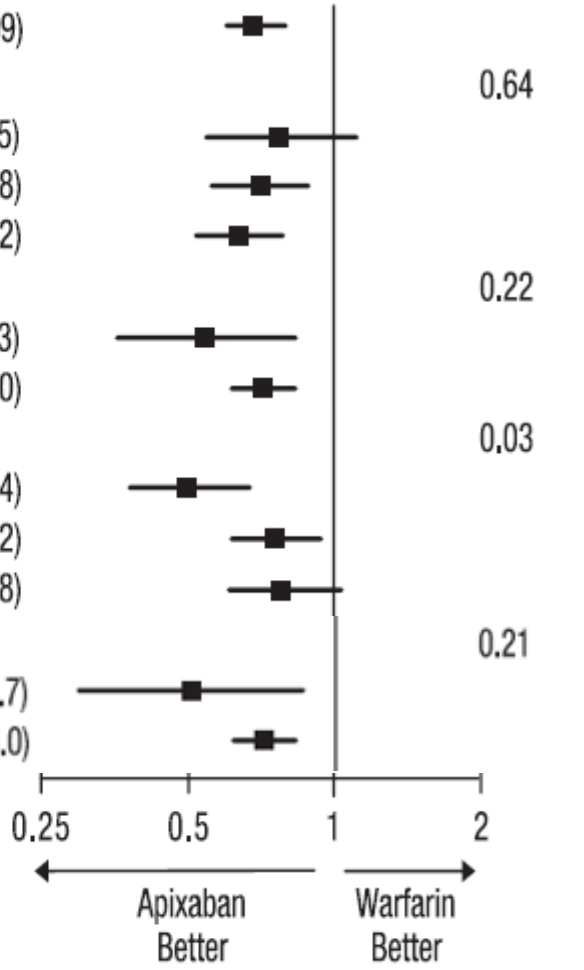
Special Populations
Consistent Safety Results in Populations with Modest PK Effects

Effect of Specific Populations on PK of Apixaban



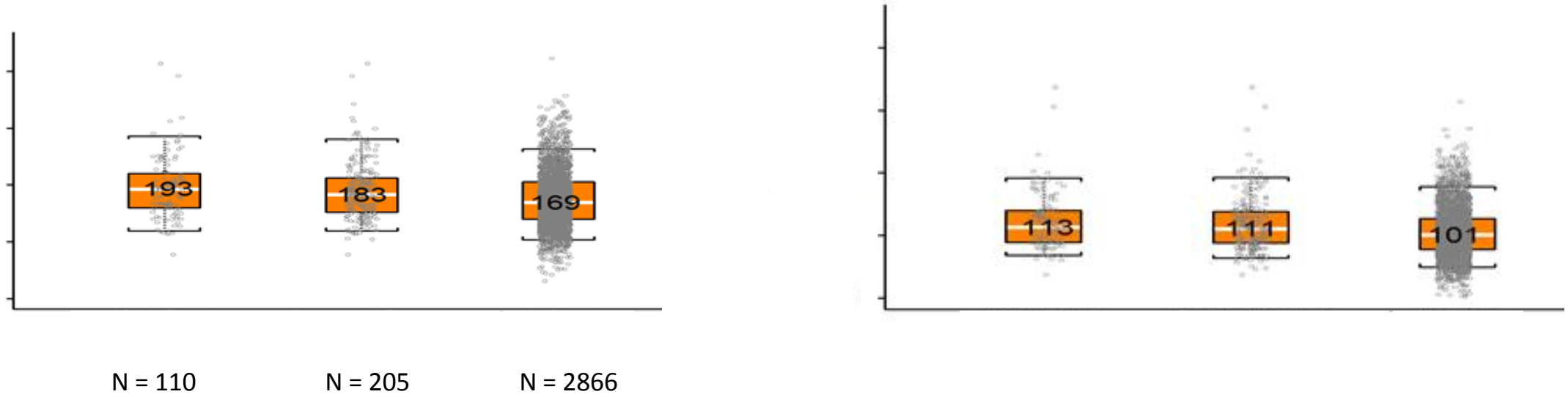
Major Bleeding by Subgroups in ARISTOTLE

Subgroup	No. of Patients	No. of Events (% per yr) Apixaban	Warfarin	Hazard Ratio (95% CI)	P-value for Interaction
All Patients	18140	327 (2.13)	462 (3.09)		
Age					0.64
<65 yrs old	5455	56 (1.2)	72 (1.5)		
≥65 to <75 yrs old	7030	120 (2.0)	166 (2.8)		
≥75 yrs old	5655	151 (3.3)	224 (5.2)		
Weight					0.22
≤60 kg	1978	36 (2.3)	62 (4.3)		
>60 kg	16102	290 (2.1)	398 (3.0)		
Level of Renal Impairment					0.03
Severe or Moderate	3005	73 (3.2)	142 (6.4)		
Mild	7565	157 (2.5)	199 (3.2)		
Normal	7496	96 (1.5)	119 (1.8)		
Apixaban Dose					0.21
2.5 mg BID or placebo	826	20 (3.3)	37 (6.7)		
5 mg BID or placebo	17314	307 (2.1)	425 (3.0)		



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

Population PK model predicted Cmax and Cmin for Subjects in ARISTOTLE with or without Bleeding Events



N = 110 N = 205 N = 2866

- 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

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 dose 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
- May be appropriate for any anticoagulant with dose-related safety concerns
  - Urgent surgery or invasive procedure
  - Bleeding or other need for reversal agent or antidote

Appropriate Measurement of Apixaban

- *“The Rotachrom® Heparin chromogenic assay was used to measure the effect of apixaban on FXa activity in humans during the apixaban development program. A concentration-dependent increase in anti-FXa activity was observed in the dose range tested and was similar in healthy subjects and patients with AF. This test is not recommended for assessing the anticoagulant effect of apixaban.* - Eliquis USPI

- *”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 [5th, 95th Percentile]	
Prevention of VTE: elective hip or knee replacement surgery		
2.5 mg BID	77 [41, 146]	51 [23, 109]
Prevention of stroke and systemic embolism: NVAF		
2.5 mg BID*	123 [69, 221]	79 [34, 162]
5 mg BID	171 [91, 321]	103 [41, 230]
Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE		
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 hospitalizations 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 PK and PD 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 favorable 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