Anticoagulant-Induced Bleeding and Reversal Agent Think Tank: An Overview of the Issues

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Disclosure

• Dr. Kowey has consulted for several companies involved in the development of NOACs and reversal agents including BI, J&J, BMS, Pfizer, Daiichi-Sankyo, Portola, Merck, AZ

• More importantly, Dr. Kowey prescribes anticoagulants and has had to deal with the consequences regularly
Frank A. Clark

“If you find a path with no obstacles, it probably doesn’t lead anywhere.”
PK/PD Parameters to Inform NOAC Dosing

• Axiomatic that individualized dosing improves outcomes
• Question brought into focus during edoxaban review and recent dabigatran publication
• Issues include feasibility of metric and offset of patient acceptance
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• Lively exchange of ideas
• Consensus on gravity of the issue
• Agreement that availability would increase utilization of OACs
• Initial discussions regarding study sequencing and level of evidence
Reality

• Short half-life of NOACs reduces the priority for reversal in clinical practice
• Despite the lack of an antidote, NOACs have been associated with a reduced risk of fatal and intracranial hemorrhage
• Availability of an antidote would improve “perception” of safety and thus utilization
The Current Paradigm

• General management principles
• Specific measures (e.g. PCCs)
• Adjunctive measures (e.g. tranexamic acid)
• Inability to inform and educate based on labeling
Novel Reversal Agents in Development

• Andexanet alfa
• Idarucizumab
• PER977 (ciraparantag)
Development questions for consideration

• Indications
• Dosing
• Outcomes
• Rebound
• Off target effects
• Logistical issues
Trial Challenges

• Preservation of equipoise
• Informed consent
• Patient recruitment
• Selection of endpoints
A path forward without an outcomes trial if…

• Excellent pre-clinical evidence
• High quality PK/PD data
• No severe safety issues in human dosing
• High quality post-marketing data can be collected
Why are we here?

• To discuss informed NOAC dosing in light of recent questions about “one dose fits all.”
• To define the data elements deemed essential in a new reversal paradigm
• To delineate data sources to inform the safety and effectiveness of new agents once they are generally available
Erich Fromm

“The task we must set for ourselves is not to feel secure, but to be able to tolerate insecurity.”