

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.”



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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



April 22, 2014: Reversal Agent Think Tank

- 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



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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



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Novel Reversal Agents in Development

- Andexanet alfa
- Idarucizumab
- PER977 (ciraparantag)



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Development questions for consideration

- Indications
- Dosing
- Outcomes
- Rebound
- Off target effects
- Logistical issues



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Trial Challenges

- Preservation of equipoise
- Informed consent
- Patient recruitment
- Selection of endpoints



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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



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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



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Erich Fromm

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



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