Discussion: ANNEXA™-R Part 2: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial Demonstrating Sustained Reversal of Rivaroxaban-Induced Anticoagulation in Older Subjects by Andexanet alfa (PRT064445), a Universal Antidote for Factor Xa (fXa) Inhibitors.

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### Disclosures for Jerrold H Levy, MD, FAHA, FCCM

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Presentation includes discussion of the following off-label use of a drug or medical device: Yes
Why is reversal important?

- Increases the safety margin of pharmacotherapy, esp anticoagulants
- Facilitates management of critically ill patients who bleed or need procedural intervention
- Provides new management strategies for patient care, bridging, and new paradigms for management
Anticoagulation Reversal Strategies

• Inorganic molecules that bind non specifically to Rx: PER977 (by hydrogen bonding?)

• Biologic molecules that are decoys and bind specifically to Rx: Andexanet alfa

• Biologic molecules that bind non specifically as polyionic/cationic interactions: protamine, rPF4

• MoAbs made to specifically bind to Rx: Idarucizumab for dabigatran (PRAXBIND), MEDI2452 for ticagrelor

• Procoagulant proteins: PCCs, rFVIIa
What does this study add?

▸ Andexanet rapidly reduced anti-fXa activity, restoring thrombin generation, normalizing coagulation parameters post-bolus and for the 2 hr-infusion in older subjects aged 50-73.

▸ The infusion is important for maintaining normal coagulation parameters with the PK/PD characteristics.

▸ This study supports the importance of andexanet as a specific reversal agent for all antiXa agents.
What don’t we know?

▸ Is 2 hr reversal sufficient and facilitation of hemostasis in urgent/emergent reversal?

▸ Will we need a longer infusion for patients who require emergency surgery/procedures or continue to bleed?

▸ What other adjuncts may be needed as part of therapy for bleeding and hemostatic resuscitation in all DOAC patients in addition to specific reversal Rx?
Despite the safety of DOACs, reversal strategies are needed for emergencies when they occur.

Andexanet reverses DOACs but also LMWH, a ubiquitous hospital anticoagulant that are needed

Current studies in bleeding patients will further define the role of andexanet and Xa reversal (Phase 3b/4 study (ANNEXA-4))