

## American Heart Association (AHA) Scientific Sessions 2014

### Progress in Development of Reversal Agent for New Oral Anticoagulants

**Chicago** - A reversal agent for a new oral anticoagulant has been reported to produce near complete normalization of all coagulation parameters in a study in healthy older adults, with no evidence of antibody formation, confirming the results of earlier proof-of-concept studies. This is the first report of Phase 3 data showing rapid reversal of anticoagulant activity with a reversal agent.

New oral anticoagulants (NOACs) have become available as potential replacements for warfarin for reduction of the risk of stroke and systemic embolism in nonvalvular atrial fibrillation and treatment of arterial and venous thromboembolism. Unlike warfarin, the NOACs do not require routine blood monitoring, they can be used at fixed doses, and they do not have major drug or food interactions. In addition to convenience, there is increasing evidence that the NOACs are equally or more effective than warfarin, while bleeding rates are comparable or even improved. However, they are limited by the lack of a specific antidote to reverse anticoagulation in cases of serious bleeding episodes or prior to urgent/emergency surgery.

#### ANNEXA-A Study

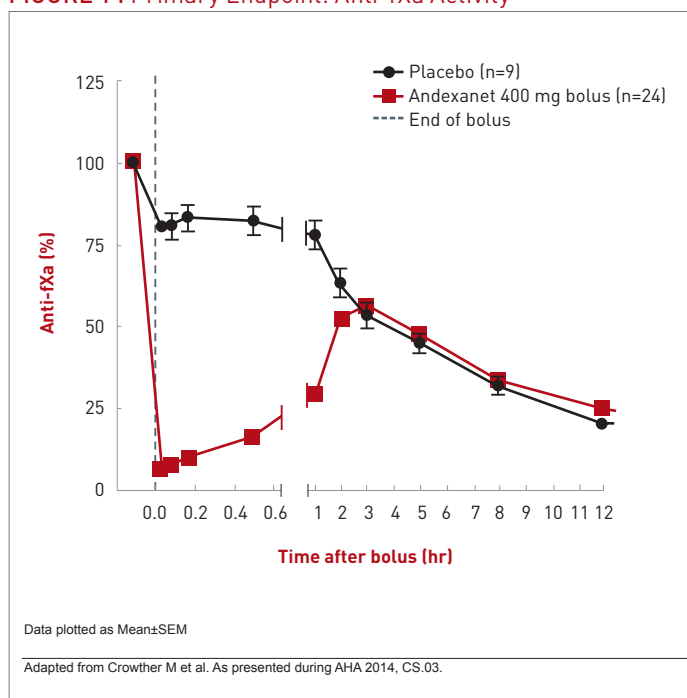
Promising clinical data for a reversal agent for the NOAC apixaban, an oral factor Xa (fXa) inhibitor, were presented by Dr. Mark Crowther, McMaster University, Hamilton, Ontario. Andexanet alfa (andexanet) is a modified, recombinant human fXa molecule that acts as an fXa decoy and reverses fXa inhibitor-mediated anticoagulation, Dr. Crowther explained.

In Phase 2 proof-of-concept studies, andexanet was shown to rapidly and significantly reverse the anticoagulant activity of apixaban 5 mg PO. The ongoing ANNEXA-A study represents the next phase in development of this agent with apixaban. In Part 1 of the study, 33 subjects (mean age 59 years) received apixaban 5 mg PO BID for 4 days. Patients were randomized (3:1) to receive a single bolus infusion of andexanet 400 mg IV or placebo administered on Day 4, 3 hours following the last apixaban dose (approximate apixaban C<sub>max</sub>).

"Immediately before the infusion of the andexanet there was very significant inhibition of coagulation and immediately after infusion of the antidote there was almost complete reversal," Dr. Crowther reported. "The product is known to have a short half-life, so after 1 hour there was a reinstatement of the anticoagulant effect, and by 3 hours the anti-fXa effect had returned to what would be expected if the patients had not received the reversal agent." All

the andexanet patients achieved  $\geq 90\%$  reversal, with a 94% change in anti-fXa activity from baseline to nadir, the primary endpoint of the study ( $P < 0.0001$ ) (Figure 1).

**FIGURE 1 | Primary Endpoint: Anti-fXa Activity**



Secondary efficacy endpoints were also met, including change in free apixaban concentration from baseline to nadir and change in thrombin generation, from baseline to peak (both  $P < 0.0001$ ), with restoration of thrombin generation to baseline in 100% of andexanet subjects (no rebound effect on thrombin generation after andexanet and/or apixaban were cleared). Apixaban-induced prolongation of activated clotting time (ACT) was corrected to the baseline range.

All subjects completed the study. Consistent with prior studies, no serious adverse events were reported. "No thrombotic events have been seen in this or any prior projects," Dr. Crowther confirmed. No antibodies to either factor X or fXa were detected.

Part 2 of ANNEXA-A will study andexanet 400 mg administered as bolus, followed by a 2-hour 4 mg/min infusion or placebo, to demonstrate that prolonged reversal can be sustained with continuous infusion after bolus. In addition, a confirmatory study in bleeding patients will be initiated at the end of 2014/early 2015, Dr. Crowther said.

Commenting on the study, AHA discussant Dr. Linda Shore-Lesserson, Hofstra North Shore-LIJ School of Medicine, Hempstead, New York, re-emphasized the need for reversal agents during surgical interventions. "These agents are here to stay – we are not going back in time," she declared. ●

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