Assessing Efficacy and Safety of NOAC Antidotes:

Post-marketing requirements, indications and their tracking, and appropriateness of usage.

Considerations From A Clinician’s Standpoint

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Sometimes we need to be able to respond more quickly!
Background

- There is a long history of use of anticoagulation reversal strategies in clinical practice.
  - Clinicians often rely on their use in patients with significant bleeding.
- Accordingly, most clinicians feel that for the NOACs, an antidote must be developed and is urgently needed to stop bleeding more rapidly than just allowing drug washout.
  - Despite the fact that NOAC half-lives are short – and similar to the Vit K time course of action.
- Assuming such development, the circumstances for its use, the sites for its administration, acceptable costs, and post-marketing tracking still have to be clarified.
Background

• Some might reasonably feel that an antidote may not be necessary.
  – Despite the absence of a NOAC antidote, life-threatening/fatal bleeding was significantly lower on NOACs than on warfarin in each of: RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE-AF.

• However, fatal and near-fatal bleeds did occur and, with an antidote, we could have done even better.

• Hence, clinicians in practice, for both patient care and medico-legal reasons, strongly desire a NOAC antidote.
Post-Marketing Considerations: A Clinician’s Viewpoint

- If NOAC antidotes are released, post-marketing requirements will be appropriate to put in place:
  - Pre-release studies have been small, and may not reflect the potential spectrum of adverse effects that could occur upon large-scale use. And, pre-release studies have shown reversal of anticoagulation effects, but that may or may not translate into measurably improved major clinical outcomes in bleeding patients or other important clinical scenarios. **Phase 4 studies should be mandated.**
  - Indications will need to be clearly defined and limited – especially before large-scale efficacy and safety data is known and given anticipated significant costs.
  - A system to verify appropriate use would be desirable, as well as one to assess any demographic, socio-economic, or other differences that may arise in use, safety, or efficacy.
CLINICAL CIRCUMSTANCES MOST LIKELY TO REQUIRE A NOAC ANTIDOTE SHOULD PROVIDE THE SETTINGS FOR POSSIBLE PHASE 4 TRIALS
Clinical Circumstances Most Likely to Require a NOAC Antidote:  
*Settings for Possible Phase 4 Trials*

- Emergency:

- Urgent:

- Non-elective surgery / intervention:
Clinical Circumstances Most Likely to Require a NOAC Antidote: 
*Settings for Possible Phase 4 Trials*

- **Emergency:**
  - Life-threatening bleeding, such as:
    - Intracerebral (if treated early enough), perforation of major vessel, aneurysm rupture,…

- **Urgent:**
  - Severe but not immediately life-threatening bleeding, such as:
    - Ongoing high-transfusion requirement, pericardial with tamponade, subdural, other specific sites…..
Clinical Circumstances Most Likely to Require a NOAC Antidote:
Settings for Possible Phase 4 Trials

• **Before, during, or following *non-elective* surgery/intervention:**
  - Patient has ongoing but non life-threatening bleeding pre-procedure that would prohibit the procedure unless stopped.
  - Patient is stable on a NOAC before the procedure but the procedure has a moderate or high bleeding risk.
  - Patient is stable on a NOAC before a procedure with a low bleeding risk, but a bleeding complication does develop intra-procedure (e.g., perforation or tear of heart or vasculature).
  - Patient is re-anticoagulated too soon post-procedure and begins to bleed significantly.
Information Needed re: Trial Design and Indications

• Dosing regimen(s) and Endpoints.

• Endpoint issues: how strong does the evidence have to be?
  – Does bleeding stop sooner than it would simply by withholding the NOAC and providing supportive care plus active procoagulants.*
  – Is non-elective surgery safe earlier than it would be in the absence of the antidote….and how to judge this.
  – Are there objective and measurable major outcome benefits, such as mortality, transfusion requirements, length of stay, major morbidity endpoints (stroke score, etc.), cost…..

*Assumes that the bleeding site will be directly addressed if possible
Phase 4 Trials Will Also Have To Assess Safety:

- **Standard treatment-related adverse events:**
  - Mortality and major morbidity
  - Hemodynamic tolerance
  - Symptomatic complaints
  - Adverse laboratory changes

- **Immunogenic adverse events** — *a potentially critical issue*:
  - Will there be (and how often) immunogenic reactions such that repeated dosing cannot be given (similar to that with streptokinase).
    - No reported signal so far — in limited numbers of patients and repetitions.
Possible Phase 4 Studies to Assess Efficacy and Safety

A Clinician’s View

• Prospective, randomized, double-blind, trial:
  – Placebo-controlled: Not ethical in this setting from a clinical standpoint.
  – Against activated PCC +/- other replacement factors:

• Surrogate outcomes: e.g., more rapid normalization of laboratory measurement of coagulation function:
  – Not necessarily clinically meaningful regarding more rapid termination of bleeding or other beneficial clinical outcomes (e.g., mortality, etc.).
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• **Registry:**
  – Only of patients given the NOAC antidote:
    • With no comparison group, determination of clinical benefit will not be more than anecdotal.
  – All bleeding patients:
    • There will be far more patients who bleed but do not get the antidote than those who do.
    • Would require a case-controlled comparison of antidote–treated patients and those who are not so treated.
  – All patients on NOACs who require non-elective surgery, with comparison of clinically-determined outcomes, such as bleeding, Tx, ICU stay, hospital LOS, mortality, etc. in a case-controlled comparison.
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**Clinically Feasible in a 1-3 yr time frame**
Possible Phase 4 Studies to Assess Efficacy and Safety

- Database Interrogation
  - EMR: in-hospital pop-up screens whenever a bleed occurs on a NOAC
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  - Correlation with hospital discharge summary events or with insurance or other data sets that incorporate such outcomes events and treatments used.
  - Since major bleeds on NOACs severe enough to require an antidote are infrequent, use of large databases will be necessary to answer some of the questions we need to ask about efficacy and adverse events in actively bleeding patients (in contrast to prospective trials or registries which will be of most use in assessing objective endpoints in frequent events, e.g., surgical/interventional settings).
Additional Clinical Issues

- Where to administer:
  - Emergency Room
  - ICU
  - Ambulance
  - Office upon first contact

- Should any tests be followed during, after administration:
  - Coagulation parameters? Which?

- Will cost be prohibitive?

- How much use will there be for less-than-indicated circumstances?
  - And how to track it and limit it.
    - Limitations can be achieved via price and control of available locations.
Anticoagulation by warfarin can be reversed by low-dose intravenous or oral vitamin K over a 24-hour period (Figure). However, the rate at which anticoagulation is reversed depends on the route of administration of vitamin K. If rapid warfarin reversal is required, the American College of Chest Physicians (ACCP) guidelines suggest the administration of vitamin K (≤5 mg) orally, with the expectation that a reduction of the INR will occur in 24 hours. In patients with serious bleeding and elevated INR, regardless of the magnitude of the elevation, the ACCP guidelines recommend holding warfarin therapy and administering vitamin K (10 mg) by slow IV infusion supplemented with fresh frozen plasma, PCC, or rFVIIa, depending on the urgency of the situation.

Figure. Oral vitamin K can take up to 24 hours to reverse the anticoagulant effect of warfarin.