Novel oral anticoagulants and reversal agents: Considerations for clinical development

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This white paper provides a summary of presentations and discussions that were held at an Anticoagulant-Induced Bleeding and Reversal Agents Think Tank co-sponsored by the Cardiac Safety Research Consortium and the US Food and Drug Administration (FDA) at the FDA's White Oak Headquarters on April 22, 2014. Attention focused on a development pathway for reversal agents for the novel oral anticoagulants (NOACs). This is important because anticoagulation is still widely underused for stroke prevention in patients with atrial fibrillation. Undertreatment persists, although NOACs, in general, overcome some of the difficulties associated with anticoagulation provided by vitamin K antagonists. One reason for the lack of a wider uptake is the absence of NOAC reversal agents. As there are neither widely accepted academic and industry standards nor a definitive regulatory policy on the development of such reversal agents, this meeting provided a forum for leaders in the fields of cardiovascular clinical trials and cardiovascular safety to discuss the issues and develop recommendations. Attendees included representatives from pharmaceutical companies; regulatory agencies; end point adjudication specialist groups; contract research organizations; and active, academically based physicians.

There was wide and solid consensus that NOACs overall offer improvements in convenience, efficacy, and safety compared with warfarin, even without reversal agents. Still, it was broadly accepted that it would be helpful to have reversal agents available for clinicians to use. Because it is not feasible to do definitive outcomes studies demonstrating a reversal agent's clinical benefits, it was felt that these agents could be approved for use in life-threatening bleeding situations if the molecules were well characterized preclinically, their pharmacodynamic and pharmacokinetic profiles were well understood, and showed no harmful adverse events in early human testing. There was also consensus that after such approval, efforts should be made to augment the available clinical information until such time as there is a body of evidence to demonstrate real-world clinical outcomes with the reversal agents. No recommendations were made for more generalized use of these agents in the setting of non–life-threatening situations.

This article reflects the views of the authors and should not be construed to represent FDA's views or policies. (Am Heart J 2015;169:751-57.)

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Submitted March 23, 2015; accepted March 23, 2015.

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0002-8703

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http://dx.doi.org/10.1016/j.ahj.2015.03.010

Anticoagulation is an important standard therapeutic approach to cardiovascular disease. As an example, in patients with atrial fibrillation (AF), anticoagulation is known to reduce the reported 2% to 18% annual risk of embolic stroke for patients with a CHADS score of 1 to 6 by two-thirds [1,2]. Despite its proven benefit, as of 2007, only approximately 60% of patients with AF were prescribed warfarin therapy [3]. Until recently, warfarin has been the only available oral anticoagulant exhibiting a positive benefit-risk profile when the extent of anticoagulation is carefully monitored and managed with dose adjustments. However, safe and effective use of warfarin includes accepting several days delay in onset and offset of effect and pharmacokinetic/pharmacodynamic (PK/PD) variability including many food and drug interactions, which complicate maintenance of the international

normalized ratio (INR) within the therapeutic range and limit more widespread use. Although underprescribed in qualified patients overall and complex to titrate, when necessary, the effects of warfarin can predictably be reversed using pathways mediated by vitamin K or more directly through administration of fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC).

The global introduction of several novel oral anticoagulants (NOACs) has recently transformed the clinical practice of oral anticoagulation. Currently approved agents include dabigatran, rivaroxaban, apixaban, and edoxaban (listed in order of US approval for stroke prevention in nonvalvular AF [NVAF] patients). Significant advantages of NOACs include the following: (1) more predictable PK/PD profile and reduced susceptibility to food and drug interactions facilitating consistent, predictable anticoagulation levels without the routine coagulation monitoring required with warfarin; and (2) relatively rapid onset and offset of action, which obviate bridging therapies such as heparin and can facilitate management of patients requiring surgery or interventions.

Novel oral anticoagulant safety and efficacy have been established in several large phase 3 clinical trials. Compared with warfarin therapy, NOAC efficacy is noninferior or superior for stroke prevention in patients with NVAF, with similar or lower levels of major bleeding [4-7]. A meta-analysis of the phase 3 trials comparing NOACs with warfarin for stroke prevention in 71,683 patients with AF revealed a 19% decrease in stroke or systemic embolism risk associated with NOAC therapy (relative risk [RR] 0.81; 95% CI 0.73-0.93; $P < .001$), mainly driven by a 51% reduction in the risk of hemorrhagic stroke (RR 0.49; 95% CI 0.38-0.64; $P < .001$) [8]. Intracranial hemorrhage was reduced by 52% (RR 0.48; 95% CI 0.39-0.59; $P < .001$), and all-cause mortality was reduced by 10% (RR 0.90; 95% CI 0.85-0.95; $P = .003$). With NOACs, the risk of gastrointestinal hemorrhage was increased relative to warfarin (RR 1.25; 95% CI 1.01-1.55; $P = .04$). With the net benefit of the NOACs established and the convenience of fixed dosing without routine coagulation monitoring, the NOACs are poised to replace warfarin with improved clinical benefit, more manageable compliance, and lowered risks in many patients [9].

Risk of bleeding in patients with anticoagulation

The major side effect of anticoagulation is bleeding. Over a 12-month period ending in June 2013, there were approximately 6.8 million patients taking anticoagulants in the United States, of whom approximately 345,000 (5.1%) presented to the emergency room with a bleeding event. Approximately 228,000 of those patients warranted hospital admission [10]. Patients with major bleeding during oral anticoagulant treatment are also at an increased risk for subsequent death and thrombotic events. The risk is similarly elevated independent of the oral anticoagulant used [11].

Whereas warfarin anticoagulation can be reversed, there are no specific reversal agents currently available for the NOACs. Despite the fact that the need for reversal of any anticoagulant is relatively rare and the rapid offset of the NOACs obviates reversal in most situations, antidotes for the NOACs would be beneficial to manage patients who require urgent surgery or interventions and to treat those with life-threatening bleeds.

Current clinical practice suggests an overemphasis by physicians and patients on the impact of (gastrointestinal) bleeding versus the risk of stroke. Of an estimated 4 million Americans with AF, as many as half, or 2 million, are not being treated with oral anticoagulants. These patients have an average annual stroke rate of around 5%, and at least two-thirds of these 100,000 strokes could be prevented. The case fatality rate for gastrointestinal bleeding on anticoagulants (of patients with a major bleed, ~5% died) is much lower than for ischemic stroke off anticoagulants (~25%). And, in contrast to strokes, gastrointestinal hemorrhages rarely lead to any ongoing disability. There is a notable treatment paradox associated with aging, an independent driver of the CHADS score, with even less likelihood of therapeutic anticoagulant use despite a greater likelihood of stroke. Formal decision analyses make clear that for AF patients, the health impact of increased bleeding risk is far outweighed by the reduction in stroke risk. Although NOACs provide good clinical outcomes in stroke prevention, serious bleeding remains a major concern for patients and physicians. The availability of specific reversal agents for the NOACs would improve the confidence of clinicians and patients in these new agents and encourage an increase in appropriate stroke preventive therapy for patients with NVAF. Insofar as there are many patients in the United States who are at risk for stroke and who are not receiving oral anticoagulation, thousands of strokes per year could be prevented in patients with NVAF. In the absence of a predicate NOAC reversal agent, the pathway for approval of a new drug for this use remains largely undefined.

To address this unmet need, a Food and Drug Administration (FDA)/Cardiac Safety Research Consortium (CSRC)-sponsored Think Tank was convened at the FDA White Oak Headquarters in April 2014 to discuss reversal strategies for the NOACs and to provide an update on the status of specific NOAC reversal agents that are in clinical development. The Think Tank discussion focused on understanding the need for NOAC reversal agents in clinical practice and the considerations for regulatory approval of such agents. The characteristics of 3 NOAC reversal agents currently in development were discussed, including a Fab fragment that specifically targets the thrombin inhibitor dabigatran (idarucizumab); a factor Xa decoy that targets factor Xa inhibitors (andexanet alfa); and PER977, an agent that antagonizes multiple anticoagulants.

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