

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.

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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.

Table I. Principles and measures for management of anticoagulant-related bleeding

- General principles
 - Stop anticoagulant
 - Hemodynamic and hemostatic resuscitation
 - Volume replacement
 - Local hemostatic measures
 - Check coagulation tests/platelets/fibrinogen/renal function
 - Blood product/coagulation factor/platelet replacement if indicated
 - With uncontrollable hemorrhage, use a massive transfusion protocol to keep up with bleeding
- Specific measures
 - VKA/Oral Xa inhibitors: PCCs
 - Dabigatran: activated PCCs, hemodialysis
- Adjunctive measures
 - Consider antifibrinolytics—tranexamic acid

Abbreviation: VKA, Vitamin K antagonists.

Current strategies for managing bleeding in the presence of anticoagulation

The complexity of managing major bleeding events in anticoagulated patients requires a dedicated and informed team of clinicians. Anticoagulation reversal presents a risk for thrombotic events such as stroke, and so studies of reversal agents have to take this hazard into account. This reflects the underlying prothrombotic condition for which anticoagulation was initially prescribed as well as the reversal agent administration, which may activate the coagulation cascade.

Currently available potential strategies to manage bleeding in the presence of warfarin

The goal in the bleeding patient is to improve the clinical situation and not just to restore the coagulation tests to normal. The general principles for management of anticoagulant-related bleeding apply to all agents (see [Table I](#)). In the particular situation of warfarin-associated bleeding, PCC or FFP in combination with vitamin K can be administered to replace the missing functional clotting factors. Some hospitals use FFP; however, PCC is often preferred because it lowers the INR more rapidly, more completely, and without the added risks of transfusion reactions and excess volume [12]. When reversing warfarin, concomitant vitamin K should be administered because of warfarin's long half-life. Without the use of PCC, vitamin K and FFP can take at least 12 to 24 hours to lower the INR into the reference range [13].

Currently available potential strategies to manage bleeding in the presence of NOACs

While 4-factor PCCs may have potential to reverse bleeding with NOACs based on their ability to increase levels of factors II, VII, IX, and X, there are insufficient data to conclude that reversing NOAC effect based on laboratory test results correlates with improved clinical outcomes. The available data are limited and, although encouraging, come from a small number of case reports and studies performed

on animals or healthy human volunteers in which laboratory coagulation parameters were monitored before and after PCC administration. In some animal models, bleeding is attenuated with PCC even without restoration of global tests of coagulation to control values. However, in the absence of a true antidote for any of the NOACs, PCCs should be considered as part of a multimodal approach to management of major bleeding episodes in NOAC-treated patients with life-threatening bleeding along with hemodynamic and hemostatic resuscitation. Their potential prothrombotic effects also need to be considered.

In addition, whereas NOACs may prolong the prothrombin time (PT) or activated partial thromboplastin time (aPTT), the extent of their effect on these assays is highly reagent specific. Prothrombin time and aPTT do not accurately reflect the mechanism of hemostasis *in vivo*; therefore, even if a particular assay is prolonged by a NOAC, administration of a nonspecific prohemostatic agent that improves or restores hemostasis in the patient may not have a commensurate effect on the PT or aPTT. Such prohemostatic agents include PCCs, activated factor VII (FVIIa), and factor VIII inhibitor bypassing activity. In contrast, it is likely that a true antidote that specifically binds and inactivates its target NOAC would also reverse that drug's effect on PT or aPTT. This could make it easier to monitor the effects of the antidote.

Recombinant FVIIa (rFVIIa) is a prohemostatic agent and is only partially effective for NOAC reversal in most experimental models. Furthermore, the risk of thrombotic complications is likely to be higher with rFVIIa versus PCC because of the activated nature of FVII. Consequently, rFVIIa should likely be avoided in patients with severe NOAC-associated bleeding. Tranexamic acid, which acts as an inhibitor of fibrinolysis, has been extensively studied in patients undergoing surgery or in those with major trauma. Although clinical data are lacking, adjunctive tranexamic acid should be considered in patients with life-threatening bleeding in association with NOACs. Plasmapheresis may be considered for all NOACs, and for dabigatran, due to its predominantly renal excretion, dialysis can also be considered. Overall, current therapy for bleeding with NOACs should be multimodal and include hemodynamic and hemostatic resuscitation of the patient with life-threatening hemorrhage. Principles and measures for management of anticoagulant-related bleeding are summarized in [Table I](#).

Novel reversal agents in clinical development

There are currently 3 NOAC-specific reversal agents in clinical development: (1) andexanet alfa, (2) idarucizumab, and (3) PER977. Each of these agents is distinctly different in terms of specificity, mechanism of action, and impact on recognized biomarkers of anticoagulant activity.

“Andexanet alfa” is a recombinant, modified human factor Xa that is being developed as a direct factor Xa reversal agent. Modifications include replacement of the

serine residue in the active site of factor Xa with an alanine residue to eliminate its procoagulant activity and deletion of the membrane-binding domain to prevent anticoagulant activity via its incorporation into the prothrombinase complex. It serves as a factor Xa decoy that sequesters direct and indirect factor Xa inhibitors in the blood. It has been shown to rapidly attenuate the anti-FXa activity of apixaban, rivaroxaban, edoxaban, and enoxaparin and to restore thrombin generation in phase 2 studies in healthy human volunteers. These reversal effects can be sustained for up to 2 hours and possibly longer, using a bolus injection followed by a continuous infusion. Nonclinical studies have demonstrated reversal of factor Xa inhibition of betrixaban as well. Andexanet alfa has been generally well tolerated and is currently in phase 3 clinical trials (ANNEXA-A [apixaban] and ANNEXA-R [rivaroxaban]).

“Idarucizumab” is a fully humanized antibody fragment (Fab) that binds dabigatran with high affinity and specificity. Idarucizumab rapidly reverses the anticoagulant effect of a 220 mg twice daily dose of dabigatran in healthy human volunteers and is currently being evaluated in phase 3 trials. There is an immediate normalization of the dilute thrombin time after a 5-minute intravenous (IV) infusion of idarucizumab at 1, 2, or 4 g. Although there was a subsequent increase in the thrombin time with the lowest dose of idarucizumab, this was not observed at higher doses. At higher doses, normalization of the dilute thrombin time was sustained for up to 72 hours. Idarucizumab has been generally well tolerated in healthy human volunteers and is currently in clinical trials in the RE-VERSE AD study (<http://clinicaltrials.gov/show/NCT02104947>) [14].

“PER977 (ciraparantag)” is a water-soluble small-molecule nonspecific reversal agent. In preclinical testing and during testing with edoxaban in healthy male volunteers, it rapidly reversed the effect of multiple anticoagulants, purportedly via hydrogen bonding. It is currently in phase 1 to 2 clinical testing in healthy human volunteers. PER977 has a rapid onset of action (5-10 minutes) after IV administration as evidenced by rapid shortening of the whole blood clotting time in edoxaban-treated healthy volunteers. This effect was sustained for up to 24 hours with a single IV dose. PER977 has been generally well tolerated in healthy human volunteers. A phase I study in low molecular weight heparin also shows reversal of anticoagulation as measured by whole blood clotting time within 5 to 10 minutes at the same doses (100-300 mg) used to reverse edoxaban. A phase 1 reversal study for unfractionated heparin is currently underway.

Development considerations and challenges

There are several considerations for development of these new agents. Although animal models exist for attempting to predict reversal of NOAC-induced bleeding, their applicability in humans remains to be determined because of the site of bleeding (eg, closed space/open space), comorbidities, and the concomitant use of long-

Table II. Development questions for consideration

Can the reversal agents be used for management of urgent bleeding and to provide rapid reversal in patients requiring urgent surgery or interventions?
What clinical outcomes are needed to assess the efficacy of these agents?
Are different doses required for management of bleeds of varying severity?
What is the optimal IV administration duration?
How long can an infusion be safely administered (eg, potential impact on volume/pressure, immunogenicity potential)?
Are POC or rapid turn-around assays available for determination of NOAC levels before and after reversal to identify patients needing reversal and assessing the adequacy of reversal?
How much reversal of the pharmacologic effect is sufficient to stop or prevent a bleeding event?
What are the clearance mechanisms of the NOAC and the reversal agents and are there special considerations for patients with renal or hepatic failure?
What is the experience in patients taking concomitant antiplatelet agents?
Is there a potential thrombotic risk?
Are there off-target effects?
Where would these agents be stored in the hospital to ensure rapid access and appropriate use (eg, emergency department, pharmacy)?
How long after discontinuing the reversal agent infusion could anticoagulation be re-initiated?

Abbreviation: POC, Point-of-care.

acting antiplatelet drugs that may influence the reversal strategy and outcome. Therefore, in addition to the PK/PD studies demonstrating reversal of anticoagulant effects, clinical data may be required either for drug approval or for determining the optimal use of NOAC reversal agents in the setting of major bleeding. Development of NOAC reversal agents could require multiple targeted studies to determine their utility, efficacy, and safety. Potential questions for development are shown in Table II.

Because reversal agents will be infrequently used at any single institution, traditional clinical investigation strategies are difficult because of, among other issues, patient recruitment and product storage issues. In addition, limited patient availability per hospital complicates the issues of determining optimal dosing, mode of administration, and medication interaction. Of particular importance is the safety of NOAC reversal agents, that is, does their administration result in excess prothrombotic events? Because of the issues mentioned above, answering this crucial safety question through standard clinical trial approaches could take many years. The efficacy of reversal agents could also be challenging to study, as life-threatening bleeding in patients on NOACs represents a heterogeneous range of syndromes and underlying lesions and pathology. Thus, in some patients, complete reversal of the NOAC may not suffice to stop bleeding without concomitant surgery, lesion embolization, or other procedures.

There are no currently approved reversal agents for NOACs, and, as unique drug class(es), randomized trial designs might initially be considered. However, in addition to the logistic complexities mentioned above, such designs would also face complexities defining the comparator group. “Standard care” for emergency hemorrhage in patients taking NOACs could involve supportive care with

Table III. Challenges with executing a traditional randomized outcomes study for NOAC reversal agents

Definition of optimal clinical outcomes is uncertain
It will be difficult to randomize severely bleeding patients to placebo when an investigational reversal agent is available (ie, insufficient clinical equipoise would exist)
It is difficult to obtain informed consent in patients with serious bleeding
There are very few patients on anticoagulants per year per US hospital with life-threatening bleeding
There is high variability in the types of patients with severe bleeding and the kind of agent(s) that they are taking
There are a large number of confounders in assessing response to therapy (comorbidities, other concomitant agents administered, the extent of transfusion varies between centers, etc)
Anticoagulant reversal may not prevent a fatal outcome in patients with severe bleeding or major trauma

possible intervention with transfusion therapies, including hemostatic agents such as PCCs, activated PCC, or rFVIIa. There are also important ethical and practical considerations if randomization of such patients involved a placebo or blinded treatment arm. Finally, determining the most suitable primary outcome measure (eg, total blood loss, time to hemostasis, correction of pharmacodynamic markers, death, and disability) would be controversial. Challenges with executing a traditional randomized outcomes study are shown in [Table III](#). Given these challenges, from a patient-centered benefit/risk perspective, it is unclear whether delaying the availability of these agents through assessment with traditional clinical outcomes trials would impair, or would promote, the public health.

Recommended development strategies for NOAC reversal agents

What is not controversial is that adequate reversal of anticoagulation in an emergency, life-threatening bleeding patient would likely reduce immediate mortality and morbidity risk. Moreover, the availability of such agents may remove a psychologic barrier to the use of NOACs for AF and thus could indirectly promote more widespread effective stroke prevention—possibly conferring a greater impact on public health than the direct benefits attributable to NOAC reversal.

The CSRC discussion reached consensus that, for compounds to be used in the management for serious, life-threatening bleeding episodes, a prospective randomized outcomes study may not be necessary if the following conditions are met:

- The events are life threatening.
- The effects of the molecule are well characterized in nonclinical studies.
- High-quality human pharmacokinetic and pharmacodynamic data are available.
- No severe safety issues have arisen in human dosing or animal studies.

- High-quality postmarketing data will be collected (format to be determined) and made available to monitor safety and appropriate use.

The reasons that a traditional phase 3 study may be obviated if the above criteria are met are the following: (a) anticoagulant-associated life-threatening bleeding is rare, rendering a traditional randomized trial infeasible; (b) there are accumulating animal and early-stage human studies to show that the agents have the desired pharmacodynamic effects and are safe; and (c) because no other treatments exist for this highly morbid situation, a randomized trial may raise significant ethical issues.

The CSRC discussion regarding the approval pathway for NOAC reversal agents seeking a wider labeling indication such as non-life-threatening bleeds or other potential uses such as decreasing time-off anticoagulation or surgical bridging strategies was more open ended, and the role of prospective trials for such circumstances would likely vary depending on the details of the indications being sought.

The Think Tank discussants also endorsed the concept that it would be desirable for such trials to be performed for drug approval indications as well as to support the development of best practice guidelines regarding the timing of both reversing and reinstating anticoagulation to limit risk of periprocedural bleeding and thrombotic events such as strokes.

For these non-life-threatening indications, alternative approaches to the traditional phase 3 randomized clinical trials and potential approaches to comparator group and outcome end points were extensively discussed, including the following:

1. Study designs such as a stepped-wedge approach are worthy of consideration. A stepped-wedge approach randomly assigns sites to collect bleeding outcomes in patients not receiving a NOAC reversal agent followed by gradual randomized opening of sites with access to a NOAC reversal agent. A final comparison is made of patient outcomes at the 2 types of sites. It is conceivable, however, that withholding the reversal agents from sites may not be considered acceptable.
2. Registry-based trial designs [15] represent another option. For instance, long-term follow-up for key end points such as death and stroke could be collected from the Medicare claims database on all Medicare eligible patients (aged >65 years, etc) treated with NOACs. This kind of national registry backdrop could provide important efficiencies for randomized designs investigating NOAC reversal agents as well as ongoing observational data in non-randomized cohorts exposed to such therapies. Importantly, claims data could also track and capture bleeding and stroke events in Medicare eligible patients exposed to NOACs per se, giving a uniquely informative context to the understanding of outcomes

related to NOAC reversal agents. Discussion of this option also highlighted the potential for collaboration between the Center for Medicare/Medicaid Services and FDA. For example, enrollment in national medical device registries has been augmented by continuing evidence decisions, requiring data entry into the registry to obtain reimbursement for the device. This approach has resulted in registries capturing >90% of device deployments in the United States. This kind of model might be useful to ensure the capture of NOAC reversal agent use nationally, for either observational or prospective study purpose, although important differences between drug and device exposures would have to be examined further.

3. Nonrandomized studies could also be performed with various controls including historical, contemporaneous at the same center, or contemporaneous at other centers, with attempts to match for variables that predict outcome. However, these designs would be subject to various sources of confounding variables.
4. Other options include running a contemporary control group at different centers or a cohort study with NOAC reversal in one arm and vitamin K antagonist reversal in the other as a type of control (although not a particularly rigorous one). Registries and postmarketing “real-world evidence” studies could also provide supportive clinical outcome data. A postapproval registry would likely be needed to look for thrombotic events associated with NOAC reversal versus standard of care.

Both andexanet alfa and idarucizumab have received breakthrough therapy designations from the FDA, as they are “intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that they may demonstrate substantial improvement over existing therapies on one or more clinically significant end points...” (Section 506(a) of Food, Drug and Cosmetic Act, as added by section 902 of the FDA Safety and Innovation Act of 2012). Breakthrough therapy designation is important in that it provides guidance on efficient drug development and other actions to expedite review. By granting these designations, FDA recognized the importance of NOAC-specific reversal agents in the management of anticoagulation. Accelerated approval is intended for drugs or biological products for the treatment of serious or life-threatening diseases that demonstrate improvement over available therapy or provide therapy where none exists. Approval may be based on a surrogate end point that is considered reasonably likely to predict a clinical benefit. Given the challenges of studying this class of drugs in animals or in normal volunteers and given their urgent and lifesaving potential, there was consensus in the CSRC discussion that it seems reasonable to consider granting accelerated approval of these compounds. Such approval might be based, for instance, on pharmacokinetic and pharmacodynamic data

demonstrating reversal of anticoagulant action in healthy human volunteers, with the postmarketing commitment to conduct clinical studies (eg, prospective observational) in bleeding patients and thus demonstrate clinical benefit and assess safety. Although simple in concept, this approach is far from simple in execution:

- The virtue of NOACs not requiring monitoring is confounded by difficulty in assessing the extent of anticoagulant action and hence in obtaining pharmacodynamic data on NOAC reversal. This is being actively addressed by the sponsors of reversal agents.
- Clinical trials in bleeding patients are problematic as discussed above. It may be possible to pursue the various options to obtain clinical benefit data; however, given the difficulties as outlined, there is a danger that the postmarketing commitment might remain unfulfilled.

Another approach is to view the approval of NOAC reversal agents differently than the approval of active drugs, for example, to consider them as antidotes to the pharmacodynamic effects of anticoagulant drugs. Predicates in this sense could include antidigoxin antibody. Showing the drug's effect *in vivo* in the absence of safety problems such as hypercoagulability could be proposed as a basis for approval, perhaps with postmarketing commitments to obtain further and even ongoing safety data.

Finally, there was considerable discussion on the projected frequency with which NOAC reversal agents would actually be used in clinical practice. Many factors were identified in this calculus, such as patient/family expectations, availability, cost, reimbursement, medicolegal implications, and other issues. Two additional dynamics were recognized related to the use of NOAC reversal agents based on their impact on public health. First, as stated earlier, the availability of NOAC reversal agents could provide greater confidence for prescribing physicians and for patients and lead to more frequent use of NOACs in patients who would benefit from them. With such growth in use, the number of urgent bleeds relevant to NOAC reversal agents would, inevitably, grow as well. Second, the progressively aging adult population of the United States, with exponentially growing rates of senescent AF, represents a growing market for appropriate NOAC use. Again, with this growth, if patients are appropriately treated with NOACs for their protective benefit, there will be an inevitable increase in the need for reversal agents.

Conclusion

Novel oral anticoagulants provide benefit (eg, stroke prevention) that, in most NVAF patients, outweighs the risk of bleeding. Novel oral anticoagulant reversal agents, if effective, safe, and available, have the potential to both further encourage appropriate use of this therapy and to improve outcomes in patients on NOACs who have severe bleeding syndromes, with a significant impact on the

overall public health, in particular in the aging population, who has NVAF and its complications more frequently.

An expedited registration pathway for NOAC reversal agents in life-threatening situations that includes well-characterized preclinical data and robust PK/PD data including demonstration of a NOAC reversal effect in healthy subjects preregistration, supplemented with observational collection of extensive safety data and clinical outcomes in patients postregistration, present a reasonable common development pathway option that could enable earlier availability of NOAC reversal agents for the benefit of both patients and physicians. Additional clinical studies might be recommended for reversal of non-life-threatening bleeding.

References

1. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864-70.
2. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154:1449-57.
3. Shroff GR, Solid CA, Herzog CA. Temporal trends in ischemic stroke and anticoagulation therapy among Medicare patients with atrial fibrillation: a 15-year perspective (1992-2007). *JAMA Intern Med* 2013;173:159-60.
4. Patel MR, Mahaffey KW, Garg J, et al. ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91.
5. Connolly SJ, Ezekowitz MD, Yusuf S, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51.
6. Granger CB, Alexander JH, McMurray JJ, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92.
7. Giugliano RP, Ruff CT, Braunwald E, et al. ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093-104.
8. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955-62.
9. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011;123:2363-72.
10. Truven Marketscan® Commercial, Medicare Supplemental, and Medicaid Databases. Time period: January 1, 2012 to June 30, 2013. Extracted April 2014. Unpublished results
11. Piccini JP, Garg J, Patel MR, et al. Management of major bleeding events in patients treated with rivaroxaban vs. warfarin: results from the ROCKET AF trial. *Eur Heart J* 2014;35:1873-80.
12. Sarode R, Milling Jr TJ, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation* 2013;128:1234-43.
13. Levy JH, Tanaka KA, Dietrich W. Perioperative hemostatic management of patients treated with vitamin K antagonists. *Anesthesiology* 2008;109:918-26.
14. Schiele F, van Ryn J, Canada K, et al. A specific antidote for dabigatran: functional and structural characterization. *Blood* 2013;121:3554-62.
15. Lauer MS, D'Agostino RB. The randomized registry trial—the next disruptive technology in clinical research? *N Engl J Med* 2013;369:1579-81.