How has anticoagulation care changed over the past 10 years?

The past 10 years have seen an incredible advance in anticoagulation with the availability of the novel direct oral anticoagulation agents (NOACs). It is important to note that the NOACs are improvements over older agents like warfarin and even without a specific reversal agent, the drugs offer improved outcomes and better safety. However, the development of idarucizumab, a specific reversal agent for dabigatran, represents the first specific reversal agent for a NOAC. This development in my view further facilitates the ability to anticoagulate atrial fibrillation (AF) patients and provides clinicians with an increased comfort level and an additional management strategy for the infrequent need for immediate reversal.

What difference have NOACs made to AF patient care?

As a clinician who anticoagulates and treats many patients with acute and chronic atrial fibrillation, the ability to start a NOAC and have therapeutic anticoagulation in 2 to 4 hours without blood sampling has been a major breakthrough.

Why was there a desire for a reversal agent?

Having the ability to acutely reverse anticoagulation would further increase the safety margin of all anticoagulation agents. I want to emphasize that until 2013 there was no reversal agent approved in the United States for acute reversal of warfarin (prothrombin complex concentrates - PCCs), and still we do not have approved specific reversal agents for the commonly used hospital anticoagulant low molecular weight heparin, nor the widely used antiplatelet agents such as clopidogrel. Although infrequent, there are occasions where an anticoagulated patient may have an episode that requires emergency surgery. The availability of a reversal agent allows clinicians to acutely reverse the effects of anticoagulation, remove it from any management concerns, and focus on other important aspects of emergency care and resuscitation if needed.

What are NOACs performing in the real-world?

I anticoagulate a complex variety of patients with cardiovascular disease, and all anticoagulants can produce bleeding. I still see far more admissions due to bleeding from warfarin than I do from the NOACs. This I believe is in part due to the NOACs far shorter half-lives when the drug is stopped. The real-world experience with the NOACs has further demonstrated their safety and efficacy. Recent real-world experience with dabigatran vs. warfarin in over 250,000 patients has demonstrated outcome data very similar to what was reported in clinical trials, where patients were carefully managed. Adverse outcomes are more common with warfarin compared to the NOACs if the patients require emergency surgery, need other procedural interventions, or bleed. Even without a particular reversal strategy, overall outcomes are actually better with the NOACs than warfarin.
When might reversal of anticoagulation be required?

In patients requiring emergency surgery, or following acute traumatic injuries such as a fall or an automobile accident, having the ability to acutely reverse anticoagulation and remove the anticoagulant effect is an important management strategy. I think the best example of this is the impressive data from our initial experience reported in the New England Journal of Medicine, which I also presented at the European Society of Cardiology Congress 2015. Of the 36 patients who were anticoagulated with dabigatran and required emergency surgery, administration of the specific reversal agent idarucizumab resulted in over 90% of patients having normal hemostasis as determined by the surgeon during the procedure.

How do specific reversal agents compare to other types of supportive strategies?

We have recently published a guidance document from the International Society of Thrombosis and Hemostasis that makes recommendations to clinicians on when and how to use reversal strategies for the NOACS. One of the critical aspects of idarucizumab and other specific reversal agents in development is their ability to remove the anticoagulant effect of the NOAC from patients who require urgent/emergency surgery or other procedural interventions, or who are bleeding. One of the impressive aspects of idarucizumab is its ability to immediately reverse dabigatran’s anticoagulant effect, and normalize coagulation for at least 24 hours. This important effect enables procedures to take place, allows for normal hemostasis during surgery and eliminates dabigatran as a factor with acute bleeding. Standard anticoagulants can be restarted if needed at any time after idarucizumab, and dabigatran can be restarted in 24 hours. Current management strategies for warfarin and other NOACS are different. Warfarin reversal requires the use of prothrombin complex concentrates to replace coagulation factors that are decreased along with vitamin K administration, and currently there is no approved agent reversal for the other NOACs that are Xa inhibitors.

What do we know about idarucizumab?

Idarucizumab is a great example of recombinant technology and the ability to develop specific binding molecules for different drugs. This has been the focus of my research for many years and represents an important therapy for clinical management. The ability to make specific antibodies and antibody fragments directed against molecular targets and/or drugs is the marriage of immunology and pharmacology, and in my view has had a major impact on healthcare.

The advantage of idarucizumab’s ability to find and immediately bind dabigatran with a 350 fold greater affinity than dabigatran’s affinity to thrombin is important for acute reversal. The effectiveness of idarucizumab was shown in the RE-VERSE AD clinical study. In situations such as patient falls, bone fractures or emergency abdominal surgery, the drug was effective at immediately reversing the anticoagulant effect of dabigatran and facilitating surgery.

What is your personal perspective on these recent developments in anticoagulation care?

I think that reversal strategies are an evolution in the perspective and I totally agree, having specific reversal agents will further improve anticoagulation management and increase the comfort and reduce the concerns that patients and/or prescribing physicians may have regarding anticoagulation for stroke prevention in patients with atrial fibrillation.

Despite the impressive safety and improvements of the NOACs over warfarin, this increased security blanket is an important psychological advantage for physicians and patients.

I believe it facilitates more patients to take their anticoagulation for stroke prevention in atrial fibrillation.

I have been managing complex critically ill cardiovascular patients for over 30 years. I have had the privilege to help develop a variety of therapeutic strategies that I think are important to improve clinical management. A major focus of my research is developing novel strategies for anticoagulation, reversal, and management of bleeding in complex situations such as patients requiring emergency surgery, following traumatic situations, or with acute bleeding. The ability to have specific reversal agents that allow acute reversal takes important clinical management to the next level and increase the safety, adoption or use of therapies, and improves clinicians’ comfort.

Idarucizumab is truly a novel drug that provides novel paradigms for clinical management.

It has been an honor to work with other bright colleagues in this area, and to further educate clinicians about the necessary management of bleeding management in critically ill situations.