Latest anticoagulants—nuts and bolts for labs

February 2013—*The list of anticoagulants has grown in recent years, which means there's more to know about whether, when, and how to monitor. Last month in CAP TODAY, Michael Laposata, MD, PhD, spoke briefly about the newer drugs and explained how the older ones—warfarin, heparin, and low-molecular-weight heparin—work, and what that means for labs. This month, he returns to the newest of the major anticoagulants.*

He presented this information last year in an AACC webinar and again at the CAP '12 annual meeting, where he also covered antiplatelet drugs. His comments in CAP TODAY come from an edited and updated transcript of the webinar.

Dr. Laposata is the Edward and Nancy Fody professor of pathology; executive vice chair of pathology, microbiology, and immunology and professor of medicine, Vanderbilt University School of Medicine; and pathologist-in-chief, Vanderbilt University Hospital, Nashville.

In 2008, The Wall Street Journal Online followed a problem in which heparin, which had been received from China where it was made, was contaminated with another glycosaminoglycan. The coverage highlighted the process by which raw heparin was made: The company picks up barrels of pig intestines from slaughterhouses, and workers use a machine to wring the fecal material from inside those intestines. Most of us don't want our IV drugs to sit next to fecal material, but that is where heparin and LMW heparin come from. Many years earlier it had been asked: If you can make heparin shorter, how short can you make it? They realized it had to be only five sugars long. This was fondaparinux (Arixtra). It's a single chemical entity—it's going just for factor X. And this is all that's needed to back into the back of antithrombin and change that conformation. No one need worry about what the pigs are doing, and it can be made the same every time. Five sugars could be put together, cost-effectively, in a pharmaceutical operation.

Who would think that cutting several sugars off a low-molecular-weight heparin would change its pharmacokinetics much, but does it ever! One to three hours after a subcutaneous injection of fondaparinux, you get a nice anticoagulant effect—lasting about a day—and it's predominately eliminated unchanged in the urine. Patients with impaired renal function have difficulty getting rid of this drug, so it must not be given to such patients.

There is no reversal agent, and when the drug was introduced, this new concept of an anticoagulant *without* a reversal agent was frightening. It has a long half-life of about 20 hours. Fondaparinux has been used as prophylaxis, often as we have used enoxaparin (Lovenox) and dalteparin (Fragmin). It can also be used therapeutically in a higher dose.

Lepirudin (Refludan) and argatroban are direct thrombin inhibitors that are administered intravenously. Lepirudin is derived from the leech compound hirudin. How does a leech suck blood? If you were a leech on someone's skin, you would want to anticoagulate the blood so it's easier to suck it out. So leeches were killed for their anticoagulant protein and a recombinant protein was made, and that's what lepirudin is.

We can monitor it easily with a partial thromboplastin time (PTT) test (to 1.5–2.0 × mean of normal range). The drug is expensive because it's recombinant, so why use it? If a patient has heparin-induced thrombocytopenia, he or she is allergic to heparin, and anything that is heparin or looks like heparin could be trouble. That is why lepirudin and argatroban surfaced with great flourish. The half-life is one hour if you have normal renal function. In end-stage renal disease it's 52 hours on average, making it hard to compensate for a mistake of giving it to a patient with severe renal disease.

Argatroban is a synthetic chemical compound—it is not a recombination protein. It is monitored with a PTT, and it is administered intravenously.

We have to monitor it a lot, often about every six hours, to keep it in the window where the PTT needs to be (1.5 to 2.0 × mean of normal range). It's for patients with heparin-induced thrombocytopenia, and especially those with impaired renal function because this drug is removed by the liver primarily, unlike lepirudin, which has renal

elimination. This is the drug most physicians are going to use first with HIT if an intravenous line is in. The half-life is 20 minutes; that's good if you make a mistake.

If you have bad hepatic function, you can cut the dose by, say, three-quarters, and you get the PTT where you want it and you can still use it. And importantly, it's a bit forgiving, with the standard dose at 2 mg/kg per minute. So argatroban has won the battle over lepirudin for patients with HIT. As with fondaparinux and lepirudin, there is no reversal agent for argatroban.

Dabigatran (Pradaxa) is a newer drug. It inhibits factor IIa, the activated form of factor II. The drug is dabigatran etexilate, which is a prodrug that is converted in the liver to the active compound dabigatran. The antiplatelet agents Plavix and prasugrel are also prodrugs, which the liver converts into a drug that will slow blood clotting.

The RE-LY study (Randomized Evaluation of Long-Term Anticoagulation Therapy) looked at dabigatran etexilate versus warfarin and found that 150 mg of dabigatran twice daily prevented more strokes or systemic embolisms than warfarin. And there were fewer major bleeds and far fewer intracerebral hemorrhages.

The half-life is 12 to 17 hours, and it's only slightly longer at 15 to 18 hours in the elderly and others with mild to moderate renal impairment.

Here is what we didn't know much about before dabigatran was released: A lot of people (10 to 20 percent) taking dabigatran have abdominal pain. In our practice it's about 30 percent of patients. Some have even told us that as much as they do not want to return to warfarin and having INRs performed, and regulating their diets, they're doing so.

Dabigatran has a Food and Drug Administration indication for atrial fibrillation. But studies have shown a good anticoagulant effect for postoperative thromboprophylaxis and a positive effect for other conditions such as venous thrombosis—all the things warfarin is used for, so new indications for dabigatran may arise.

There is no reversal agent for dabigatran. Some have begun to say they will try recombinant factor VIIa, NovoSeven, at about $1,000 per milligram—a very expensive way to reverse dabigatran—and possibly at a less than standard dose of 90 mg/kg. Another possibility: activated prothrombin complex concentrates.

Jack Ansell, MD, of Lenox Hill Hospital in New York, who has been involved in many of the studies of the new anticoagulants, has said that a dose of VIIa that is less than the full dose of 90 µg/kg, perhaps 30 mg/kg, might be used to treat the bleeding patients. The 90 µg/kg dose is used to stop bleeding in a patient with a factor VIII inhibitor. Alternatively, hemodialysis can remove about 60 percent over two to three hours. That is not an option for the other irreversible anticoagulants.

The FDA indication for dabigatran is for prevention of stroke and systemic embolism in patients with atrial fibrillation. If under age 80, the dose is 150 mg twice daily. For patients age 80 and older, it's 110 mg twice daily. For those with severe renal impairment, it's 75 mg twice daily.

Let's say a patient goes to a party and forgets to take her Coumadin at bedtime, as it's supposed to be taken once a day. She wakes up in the morning and realizes she forgot. She can take her Coumadin, and her INR, if it was 2.5, might have gone down to 2.2 or 2.1, but she is still therapeutic. What if you have a drug where if the patient doesn't take it, she's fully coagulable at the time of the very next dose? If she forgot her dose, and the half-life is about 12 hours, she is well on her way toward normal again. And if she forgets it for a whole day, she's almost fully coagulable. It's very important that the patient not miss a dose of dabigatran. Twice daily dosed anticoagulants are more worrisome for the patients who are not highly compliant with their medications.

It's easy to convert people from low-molecular-weight heparin or warfarin to dabigatran. For LMW heparin, if you're giving it twice a day, you substitute the dabigatran when you were going to give the next dose of LMW heparin. If converting from warfarin, the INR must be less than 2.0 when the dabigatran is started.

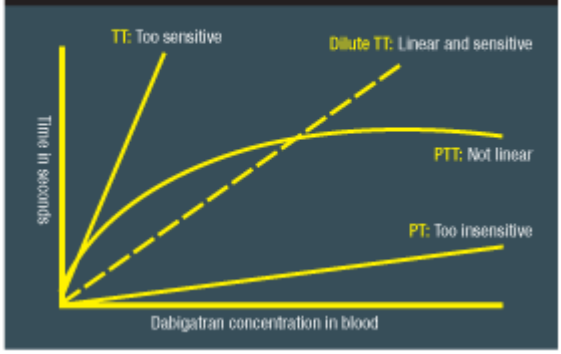
How long before surgery must dabigatran be discontinued? It's about a day for minor surgery and two days for

larger procedures or ones when a small bleed may be very dangerous. It may require bridging therapy, using a shorter-acting anticoagulant before surgery, and that is something most doctors have yet to deal with. How long after surgery before you can re-start? Six hours is a common practice.

Patients on dabigatran need not be monitored routinely. That's why some patients taking dabigatran are surprised others are still on warfarin therapy and having to still be tested for an INR value. But what happens if the patient's blood dabigatran activity is unknown—we don't use the INR for dabigatran—and he or she starts to bleed? Is it because the dabigatran level is too high? It is in this situation that a plasma dabigatran level can be highly informative. A dilute thrombin time test can be used to determine the anticoagulant effect of dabigatran because the relationship between plasma dabigatran and the clotting endpoint in the dilute thrombin time test is linear.

If you want to find out if residual dabigatran is present, because it's a direct thrombin inhibitor, the standard thrombin time is highly sensitive for residual dabigatran. A normal thrombin time test in a patient who has been treated with dabigatran indicates the drug is no longer effective.

Fig. 1 Monitoring possibilities for dabigatran with PT, PTT, and thrombin time (TT)



In the patient on dabigatran who develops a thrombotic stroke, the plasma concentration of dabigatran can be measured to determine if the patient suspected of poor compliance is taking the drug.

In **Fig. 1,** notice the thrombin time and how a little dabigatran pushes it way up. That's why if the thrombin time is normal, there's no dabigatran. You couldn't use it to monitor, however, because it is not linear through the concentration of dabigatran that you might have in the blood. A dilute thrombin time works much better. The PTT is not linear, and the PT is not sensitive.
Dabigatran costs $5.46 per day for 150-mg tablets twice a day, and warfarin is 37 cents a day. That's about $1,500 more per year than warfarin. If a large percentage of patients on warfarin were to switch to dabigatran—say 10 million people—the additional yearly cost would be $1.5 billion for the one medication switch.

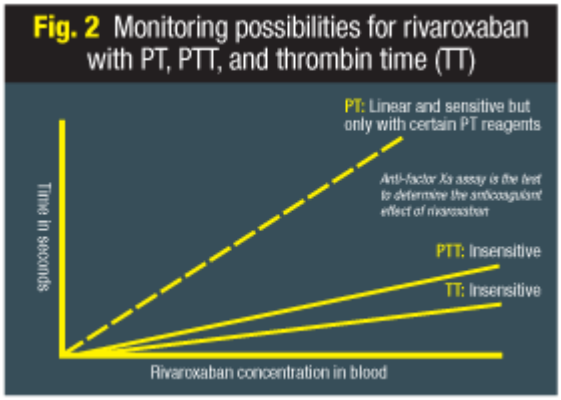
The movement from warfarin to dabigatran has been substantial: millions of users. The return of dabigatran patients to Coumadin is not negligible, but it is small. So people are definitely moving forward with this. The dietary impact of eating foods with large amounts of vitamin K (broccoli, cauliflower, chick peas, and leafy vegetables as examples) and the interaction of warfarin with other drugs can create havoc because it can make the effect of warfarin larger or smaller. The logistics of life on Coumadin are challenging, so I think that the movement will continue, though I do not think everybody will come to use dabigatran, rivaroxaban, or apixaban [see page 11]. There will still be Coumadin users, because they've been using it and doing fine with it. However, a lot of the new users are likely to begin with other drugs.

Bivalirudin (Angiomax) is delivered intravenously, it inhibits thrombin (factor II), and it has a short half-life of 25 minutes. In a patient who has severe renal impairment, the half-life is about an hour. We can give it to those who have heparin-induced thrombocytopenia and have to undergo cardiac surgery. The bypass pump has to be used, and you don't want to put whole blood through plastic and not have it anticoagulated because you can end up with clotting.

We typically don't think of it as one of our routine anticoagulants because it's monitored by an activated clotting time (ACT) rather than PT, INR, or PTT. It must be discontinued eight to 10 hours before surgery, and if we choose to continue with it postoperatively, we restart it two to four hours after surgery is completed. We monitor with the

activated clotting time because bivalirudin prolongs the PTT to its maximum value. It is very expensive: $214 per treatment.

Rivaroxaban (Xarelto) is an oral direct inhibitor of factor Xa, so we use the anti-factor Xa assay. When compared with Lovenox, which is good at preventing clots in patients undergoing total hip arthroplasty, rivaroxaban is better. The RECORD1 study (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism 1) found it to be significantly more effective than Lovenox for preventing venous thromboembolic events. It was not associated with any significant increases in major bleeding or other bleeding events. So one FDA-approved clinical indication is postoperative thromboprophylaxis for patients undergoing elective total hip or knee replacement. It has more recently been approved by the FDA for treatment of venous thrombosis, primarily deep vein thrombosis in the extremities and pulmonary embolism. Like dabigatran, it is also approved for non-valvular atrial fibrillation.



It has a half-life of five to nine hours—a little shorter than dabigatran, and the elderly have a little longer half-life at 11 to 13 hours. We don't have a good reversal agent, but there is evidence that prothrombin complex concentrates can be effective in reversing rivaroxaban. You're dealing with major firepower, strong procoagulants, when shutting off dabigatran and rivaroxaban.

For recovery from hip or knee surgery, the patient might take Lovenox for 14 days. If the patient takes rivaroxaban for 35 days, he or she runs a lower postoperative DVT risk. We want to discontinue it 22 to 26 hours before surgery. The half-life is about five to eight hours. We're still waiting four or five half-lives before surgery. After surgery, we are waiting four to six hours to restart the anticoagulant.

No routine monitoring is needed with rivaroxaban, though patients with extremes of body weight may require monitoring. The assay to use to monitor rivaroxaban therapy is the existing anti-factor Xa assay. The prothrombin time may correlate with rivaroxaban concentrations in the plasma, but it does not work for all PT reagents. There are far fewer drug interactions than with warfarin (**Fig. 2**). The thrombin time doesn't rise much either. The prophylactic dose of 10 mg per day is $5.76.

Apixaban (Eliquis), another anti-factor Xa inhibitor, has been FDA-approved for stroke prevention in patients with atrial fibrillation, only for the past few months. More to come on apixaban as we gain clinical experience.

To sum up: Determine which anticoagulant is on board. Decide how to manage the patient based on the procedure to be performed. Perform monitoring for anticoagulant effect if it's needed. For all patients, know what to do if they're bleeding, possibly because they got too much. Know what to do if they're clotting, meaning they probably don't have enough. And know what to do in the laboratory to address both of those scenarios.

The biggest challenges are the anticoagulants that have no established reversal agents, or that have a powerful reversal agent that can induce thrombosis, moving the coagulation speedometer needle quickly from bleeding all the way to thrombosis.

Find part one of Dr. Laposata's talk in the January 2013 issue of CAP TODAY.