Is It Time to Stop Using Warfarin for DVT?

By Rob Orman, MD

Any new therapy needs to be judged by multiple factors — efficacy, side effects, expense, ease of use, and reversibility. Most of us would not consider giving a new therapy to our patients if it is not as effective as the old therapy, and we also want know if the new therapy is safe, or at least no more dangerous than what we’re already using.

Then we want to know the relative cost because new therapies aren’t cheap. Bringing a drug to market costs a lot of money, which is passed along to those buying the medication: patients, insurance companies, and the government.

The question before us now is, does rivaroxaban for treatment of deep venous thrombosis (DVT) warrant changing our current treatment with vitamin K antagonists (VKAs)?

The Evidence

The main study looking at rivaroxaban treatment for DVT was by the EINSTEIN group. (N Engl J Med 2010;363[26]:2499.) About 3,500 patients with acute symptomatic DVT continued on page 10

Could Freestanding EDs Be Good for EPs?

By Gina Shaw

That was about four years ago. Today, Dr. McLaughlin has time for the gym and dinner with friends. “I see myself working a longer and more fulfilling career,” he said. “I can’t imagine a day when I will walk away from all this and be glad that I don’t have to go back again. In a heartbeat, I’d sign up all over again. I’m having fun. I love my job.”

The difference? Dr. McLaughlin no longer works in a hospital-based ED, or at least not most of the time. He still

Insured or Not, Lack of Access Drives Patients to EDs

By Ruth SoRelle, MPH

Those in and outside the health care system often blame patients for their nonurgent ED visits, labeling them medically illiterate. Some, despite all the evidence, point to this as the cause of emergency department crowding.

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were split into two groups. Group one received standard therapy with low molecular weight heparin (LMWH) and an oral vitamin K antagonist. Group two was given rivaroxaban 15 mg bid for three weeks and then 20 mg once daily for the duration of therapy, either three, six, or 12 months. This trial was supported by Bayer-Schering Pharma and Ortho-McNeil, which invariably casts a shadow of doubt on the data, but it did have good representation of the different causes of DVT, including unprovoked surgery, trauma, immobilization, estrogen, cancer, and previous venous thromboembolism (VTE).

The primary efficacy outcome was recurrent venous thromboembolism. Both groups were statistically the same: 2.1 percent for rivaroxaban and 3.0 percent for standard therapy. A combined safety outcome of major bleeding and clinically relevant non-major bleeding was the same for both groups at 8.1 percent. Major bleed rates were around one percent for both groups, which was the same major bleed rate for a follow-up study looking at rivaroxaban for PE.

But what is a “major” bleed? It was defined in these trials as clinically overt bleeding with at least a 2g/dL hemoglobin drop, bleeding that led to at least a two-unit blood transfusion; intracranial or retroperitoneal or critical site bleed; or bleeding that contributed to death.

The INR was therapeutic about 50-60 percent of the time in the EINSTEIN study of rivaroxaban for VTE, as well as in a follow-up study on PE. Would rivaroxaban have looked so good if the INR were therapeutic 100 percent of the time? We’ll probably never know. A 2011 Swedish study found the INR in therapeutic range 76 percent of the time in 18,000 patients on VKAs. How would rivaroxaban have fared against this cohort? Or would they have had higher bleeding risk?

Rivaroxaban is dosed by weight, yet LMWH is based on a fixed dose, giving a low volume of distribution. This means that most of the drug moves about in the vascular bed, not body tissue. Light (<50kg), average (70-80 kg), and heavy (>80 kg) subjects were given rivaroxaban in a pharmacokinetics study of 48 patients with a mix of men and women. Anticoagulant effect was similar between genders. A little more anticoagulant effect was seen in the light group and a little less in the heavy group but not enough to justify dose adjustment.

Should warfarin be voted out of office? Why would you vote the incumbent out of office if the new therapy is similar to the old one on recurrent VTE and bleeding? How would you campaign against each candidate if this were politics? Unfortunately for warfarin, it has a long track record, and we can bring out its dirty laundry.

Warfarin is simultaneously a great drug and a horrible drug. It’s great because it thins the blood, and it’s horrible because it makes patients bleed. And it has variable and erratic metabolism, needs frequent monitoring, and requires patients to have dietary restrictions. The INR was therapeutic (2.0-3.0) just more than half the time and low about a quarter of the time in the 2010 EINSTEIN study. This was in a clinical trial where you would expect tight control. Warfarin is a fussy drug, and your patients will need to give themselves LMWH shots until the goal INR is reached. Self-administration or clinic administration of LMWH can be a barrier to treatment. It’s expensive, and it can get really expensive if treatment becomes prolonged.

The new drug, rivaroxaban, is no worse than the old drug in efficacy and bleeding. Is it better? It’s orally dosed, and no bridging LMWH shots are needed. It has more reliable metabolism, less drug interaction, no dietary restrictions, and no monitoring. But like any new drug, a lot of dollars signs are attached. Then there’s the problem of reversibility, which is the Achilles heel of the new anticoagulants.

Cost

The cost of LMWH and warfarin for three months is about $1,060 at my local pharmacy. LMWH is $70 a dose; five days at two doses a day is $700. Warfarin for 95 days is about $10. INR testing is $44 dollars per test. The total number of tests is going to vary, but I’ll estimate eight total tests. That’s one every other week once the INR is therapeutic and some extra tests in the beginning before it is therapeutic. Say it will cost $350 for all the INR testing in a three-month period.

That’s only the money, not the other challenges that come with warfarin: restrictive diet, frequent testing, variable metabolism. It’s no secret that warfarin is metabolized differently by different people and even in the same person depending on the circumstances.

Rivaroxaban for three months costs about $1,200. The first three weeks, or 21 days, at 15 mg bid is $450. Then 60 days of 20 mg per day at $81 a pill is $759.

Reversal

The biggest concern with rivaroxaban is that its anticoagulation effects may trigger life-threatening bleeding that we cannot easily reverse. But is it really non-reversible?

What do we know about rivaroxaban reversal? A few studies give some idea on reversal, but there’s not a mountain of evidence where we can say, “Yes, we’ve got this covered.”

The rivaroxaban pharmacology basics you need to know: its half-life is five to nine hours, it cannot be dialed out, and it is 95 percent protein-bound.

Most clinicians want to know if any product can reverse rivaroxaban’s anticoagulant effect. What about protrombin complex concentrate (PCC)? The answer is, unfortunately, kind of. Possibly. Maybe.

The study most quoted about reversal of rivaroxaban looked at 12 healthy men given rivaroxaban for three days. (Circulation 2011;124[14]:1573; study supported by Sanquin.) Rivaroxaban prolonged the prothrombin time (PT) and the endogenous thrombin potential. Patients were then given Cofact, a four-factor PCC. As an aside, four-factor PCC was just FDA-approved in the United States, but is not widely available. Back to the study: healthy male subjects, cash in their pockets (you didn’t think they’d do this for free, did you?), and they’ve been taking rivaroxaban for three days: blood is thin, clotting tests are abnormal, and in goes the PCC. What happened?

PCC immediately normalized the PT. The control reversal agent was saline which, not surprisingly, did not correct the PT. We know that when PCC works, it works right away. It just did that in healthy subjects taking rivaroxaban: the PT was normal right away. The endogenous thrombin potential was also normalized by PCC but not by saline. Lab tests corrected. So far, so good. But what about actual bleeding? There are no human studies on this, but there are some animal data.

One study showed that rabbits given rivaroxaban and then PCC had improved lab tests, but their ears bled just as long. (Anesthesiology 2012;116[2]:94; the authors of this study disclosed links to one or more of these companies: Bayer HealthCare, BMS, LFB, Octapharma, Pfizer, Boehringer-Ingelheim, Leo Pharma, Sanofi-Aventis, GSK, NovoNordisk, and CSL Behring.) There was possibly underdosing of PCC in this trial but no difference between the two groups.

Another study looked at mesenteric bleeding in rats given rivaroxaban followed by PCC. (J Thromb Haemost [poster] 2009;7[Suppl 2]:370; study done by Bayer Schering Pharma.) PCC at a dose of 50 units/kg almost completely normalized bleeding time while 25 units per kilogram did not. Going back to the healthy human volunteer study, 50 units/kg of PCC was the effective dose used. PCC had no effect at 25 units/kg.

So, some animal data say PCC has little effect on bleeding, and other evidence says PCC reverses bleeding. But a rat’s gut is not a human’s brain. Can we infer that the correction of bleeding in this surrogate model applies to the catastrophic brain bleed you are seeing in your resuscitation bay? Maybe, but it’s still unknown. The evidence is better for rivaroxaban than for dabigatran. Healthy subjects in this study given rivaroxaban were also given dabigatran at another time, and PCC had no effect on the clotting tests. Some animal evidence suggests that PCC may help with dabigatran-associated bleeding.

What about our old friend FEIBA, factor eight inhibitor bypassing activity? Not everyone has PCC; but many EDs have FEIBA. Some lab data in hamsters and rabbits given rivaroxaban show that FEIBA reduced protrombin time and bleeding time.

Recombinant and plasma derived factor Xa antideses on the horizon, but they are still in testing. We’ll let you know more when and if they are ready for prime time.

Rivaroxaban v. VKAs

Consider these factors to help you decide whether to use rivaroxaban or VKAs in your patients with newly diagnosed DVT. The cost for three months is about the same. Efficacy is about
Rivaroxaban

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the same. Complications are about the same. Eight percent bleed rate and one percent serious bleed rate.

Rivaroxaban is much easier to use and VKAs have the advantage for reversibility, but it’s still a question mark. Some evidence suggests that rivaroxaban is reversible by PCC, but that research is in its infancy. PCC reverses VKA INR elevation almost immediately, but may not control the bleeding.

I can’t tell you which agent to use because there is still no right answer. I prescribe rivaroxaban and VKAs using a decision tree that involves a conversation among the patient, the primary care provider, and me. I try to make it simple for my patients by breaking it down into these factors.

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Time-Honored Tool

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predispositions that I do, words are still an intrinsic part of your work. I challenge you to think of a single therapeutic agent you use on every single patient as often as you do your words. Not only that, but this is your primary tool in every turf war, administrative issue, research publication, and interprofessional dialogue. Like the most potent medications, words are extraordinarily powerful and extraordinarily dangerous. The way we use, misuse, or confuse words is one of the most critical priorities for those working on safety improvements and the reduction of medical error.

I get twitchy every time I hear a physician say, “It’s just semantics,” “This is just wordsmithing,” or some other dismissive reference toward a thoughtful analysis of the words we use and how we use them.

In fact, words are the most ubiquitous feature of emergency medicine — bar none — and one of the most critical tools to use correctly.

With that in mind, I will be writing this column in Emergency Medicine News quarterly, and we will examine words, including the rich fields of literary criticism, linguistics, grammar, and communication psychology, and how they affect our practice of emergency medicine. Just as specialty discussions of airway management go far beyond your first-year anatomy class in medical school, I hope these discussions go far beyond your elementary school grammar class. I hope each installment will intrigue you as we examine why we use words the way we do, inspire you as we explore ways to use our words to greater advantage, and irritate you as we reveal that myths are just as prevalent in our emergency medicine verbiage as they are in our medical practice.

And we will do all that without any of the high technology trappings of modern medical practice: no ultrasound, no needleless syringes, no stethoscopes, no fiberoptics. Just a single time-honored medical tool that deserves some dusting off: words.

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