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To Monitor Dabigatran or Not: A Matter of Patient Safety

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Guest:
John Mills received a PhD in Biochemistry from McGill University in Montreal and is a Clinical Chemistry Postdoctoral Fellow at the Mayo Clinic.

Bob Barrett: This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

In October of 2010, the U.S. Food and Drug Administration approved a new oral direct thrombin inhibitor for prevention of stroke and thrombosis in patients with atrial fibrillation. This marked a new era in the development of fixed dose novel oral anticoagulants, with a hope of achieving improved safety and clinical outcomes compared to warfarin.

But fixed dose anticoagulants represent a marked departure from drugs like warfarin, where effectiveness and dose is monitored by laboratory measurements.

A paper in the May 2015 issue of *Clinical Chemistry* examined this topic in a perspective paper titled "To Monitor Dabigatran or Not: A Matter of Patient Safety."

We are joined by one of the authors of that paper, John Mills, who received a PhD in biochemistry from McGill University in Montreal and will be completing his Clinical Chemistry Postdoctoral Fellowship Training at the Mayo Clinic this July.

Dr. Mills, what assays are currently available to monitor Dabigatran as an anticoagulation drug?

Dr. John Mills: So there are actually several different assays that are available to measure Dabigatran anticoagulation. These can be broken down into maybe two or three types; those that measure thrombin activity directly; those that directly measure drug concentrations in plasma, and then those that would measure clotting times.

Two of those assays stand out as being superior to the others and those are the direct thrombin inhibitor assays as well as LC-MS/MS measurement of drug concentrations.

There have been several direct thrombin inhibitor assays which have been developed. These are based upon the

traditional thrombin time assay, with the caveat that the thrombin time assay as currently used -- traditionally used-- is actually too sensitive to measure Dabigatran so some modifications to that assay had to be made in order to be useful to measure the Dabigatran concentrations that would be clinically relevant.

To do that basically patient samples are prediluted with normal pooled plasma. And then the first actual commercial assay that was available that did this was actually not available in the US as a FDA approved test, rather only available as research only, and this assay basically used purified thrombin, basically diluted into this pooled plasma, and then this was used to dilute patient samples.

And there have been numerous studies showing that this assay correlates very well with Dabigatran plasma concentrations as measured by LC-MS/MS in patient samples.

One of the benefits of this assay is that it's readily automatable and it can be performed on most of the common instruments that would be found in the laboratories currently.

One of the limitations to this assay, where LC-MS/MS has an advantage, is that the lower limit of linearity for these assays is typically down to 15 ng/ml, whereas assays measured by LC/MS-MS can go down where it's 1 ng/ml.

And there is a growing list of reference laboratories and academic hospital labs that are now developing these assays in-house. Several of the reference laboratories offer these two assays commercially.

Bob Barrett: What sort of limitations apply to the traditional therapeutic drug monitoring in the case of Dabigatran?

Dr. John Mills: So the major limitation for therapeutic drug monitoring for Dabigatran is that if the goal is to optimize dosing to achieve a therapeutic index, there really isn't any data that's been generated that's, at least publicly available, that says how you should adjust the dose in order to target that particular therapeutic index.

And the therapeutic index itself that is in the literature has been generated by the company--it hasn't really been confirmed out there in practice yet--and it probably would require more thorough analysis to really define that therapeutic index.

Another potential problem with TDM and Dabigatran is the fact that there is a large variability in concentrations found

in a majority of the patients, both when measuring trough concentrations or measuring peak concentrations, so you can see upwards of 400 full differences across the population.

There is not a whole lot of data out there about the intra-individual variability so it's really hard to know if you do make these dose adjustments, will you be able to target that therapeutic index, and what is the appropriate therapeutic index that should be used? So there are additional studies that will be needed to perform before you can truly optimize dosing using TDM for Dabigatran.

However, that doesn't prevent using these assays to monitor the drug concentrations to just confirm compliance or to determine whether or not Dabigatran is on board in a patient prior to surgery.

Bob Barrett: Dabigatran has a reputation as a fixed dose novel anticoagulant drug that does not require monitoring. Does it live up to that reputation?

Dr. John Mills: So the answer to that is both yes and no. Yes in that, in a majority of the clinical trials to date looking at Dabigatran's performance compared to warfarin, pretty much across the board have demonstrated Dabigatran is at least non-inferior, if not superior, in its ability to prevent stroke without increasing the risk of bleeding.

However, in this context a lot of the data is looking at averages across large populations. The sub-study of the RE-LY trial, which led to FDA approval, looked at individual pharmacokinetic data and demonstrated that there is a fairly wide range of plasma concentrations across the population when using this "one dose fits all" approach.

So the "no" comes in, in the sense that there is a fraction of the population, and not necessarily only the elderly and those with impaired kidney function that we know about, where the fixed dose is not ideal. So it would seem prudent to explore the possibility that a fixed dose might not be the best option for some patients and that further benefit might actually be achieved by using personalized doses.

One of the questions that I think is important that remains to be answered is whether or not a one-time measurement of trough concentrations of Dabigatran would be sufficient to adjust doses or would more regular periodic monitoring be essential similar to warfarin?

And again, I am talking about this subpopulation of patients which have been shown to have extremely high levels of Dabigatran using fixed dose usage.

You also have to consider aspects of Dabigatran that might also be conducive to monitoring, such as patients that have acute kidney function changes, patients that are going to be undergoing invasive procedures, and then also compliance.

So one of the other important aspects in relation to Dabigatran that doesn't necessarily come to one's attention is the fact that it has a very short half-life compared to warfarin. So in the case of warfarin, where if you miss a dose, there might not be an immediate consequence, whereas if you missed a dose of Dabigatran with a half-life in a range of 12-17 hours, you could actually significantly change the state of anticoagulation simply by missing a dose. So compliance is another important reason why monitoring might actually be beneficial.

And another potential pitfall is because patients are taking Dabigatran and they are not necessarily required to seek out regular testing, they may be less likely to make regular visits to their clinician. So there is this risk that more time may elapse in these patients before potential problems are discovered and addressed.

In clinical trials where Dabigatran was tested leading to FDA approval, there was actually scheduled regular intervals throughout the trial where patients had to come in to be evaluated.

In practice this actually doesn't seem to be the case. There have been some studies in large academic settings that have demonstrated there is actually significant rates of noncompliance and patients not visiting their physician as frequently.

So there are some other reasons also why regular monitoring actually might be beneficial, particularly in some subsets of patients.

Bob Barrett: Doctor, would initial dose adjustments based on trough drug concentrations interfere with the cost benefit of novel anticoagulant drug such as Dabigatran?

Dr. John Mills: So, that's a good question. There has been extensive analysis of the cost benefits of using Dabigatran in comparison to warfarin when looking at the overall healthcare cost. But as far as I am aware, there hasn't been any comprehensive studies evaluating how this cost analysis would change if you were to incorporate the costs associated with either one-time or periodic monitoring of Dabigatran that would be incorporated into taking the drug.

In the case of warfarin, the cost of monitoring is actually more than the cost of the drug itself, because it's a generic at this point. It's a bit different for Dabigatran, where yearly costs for the drug are approximately $3,000 yearly.

So if you were to have a periodic or even one-time monitoring, that actually would be a small fraction of the total costs associated with taking Dabigatran, and of course if by monitoring you increased patient safety, less negative outcomes, you can imagine that the cost benefit would be even greater.

So it would be interesting to determine whether or not one-time monitoring or even periodic monitoring, how it would, I guess, affect the cost structure for Dabigatran.

Bob Barrett: Finally Dr. Mills, what steps could the FDA and drug makers take to improve patient safety and ensure a more transparent process going forward with the approval of future novel anticoagulant drugs?

Dr. John Mills: So, with the novel oral anticoagulant drugs there is a bit of a dilemma. The concept of a fixed dose anticoagulant that doesn't require periodic monitoring was very enticing to the FDA and of course to patients.

So given this novel concept that would allow the drug to qualify for fast track FDA approval, so there was some level of incentive for the drug makers to demonstrate that the best use of these new drugs like Dabigatran would be to compare them in studies against warfarin, where the drugs were not monitored. So you would compare Dabigatran at a fixed dose versus warfarin with regular monitoring.

The way this is set up is, it doesn't necessarily encourage the drug maker to say to the FDA, hey, we could do an even better job, improve patient safety, risk benefit profiles even further if we were to monitor the drug. So there wasn't necessarily this incentive to look at whether monitoring could further improve the drug during these clinical trials.

So in the case of Dabigatran we are now in a situation where data came out post-market after the drug was approved suggesting that dose adjustments might benefit certain patients by lowering the risk of bleeding without increasing any risks of stroke.

But again, there were no studies done post-approval, and it's unlikely in the post-market that there would be a huge willingness on the part of the drug maker to go back and revisit this. This would be fairly costly studies to perform.

So part of the problem lies in this fast track drug approval process. Another step that might be useful is, and it particularly applies to the case of Dabigatran, is that individual patient pharmacokinetic data was actually available from Phase II and Phase III clinical trials prior to its approval.

So in the RE-LY trial which led to FDA approval for this drug, this data was generated, yet it only became publicly available several years later, so well after the drug had been approved. Had this data been available earlier, there might have been a realization that hidden amongst these large population based results, there were subpopulations where pharmacokinetic modeling may have revealed that dose adjustments would dramatically improve benefit risk profile for some of these patients.

It would probably be beneficial to start this process of defining these patients and optimizing doses earlier rather than later. And again, this all assumes that the FDA would view such efforts favorably and it wouldn't interfere with approval of the drug because if it would, it would be difficult to expect drug makers to go the extra step.

Bob Barrett: John Mills is a Clinical Chemistry Postdoctoral Fellow at the Mayo Clinic and he has been our guest in this podcast from *Clinical Chemistry* on novel oral anticoagulants.

I am Bob Barrett. Thanks for listening!