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Apixaban, Anticoagulation, & Atrial Fibrillation

Introduction

Atrial Fibrillation patients have had limited choices for thromboprophylaxsis for a long time. The main contender has always been warfarin along with all of its monitoring, diet restrictions, and many drug-drug interactions. The last several years we have had some other oral options hit the market with the newest one being Apixaban (Eliquis).

Today I am going to provide an overview of this new Factor Xa Inhibitor and compare it to the other oral competitors for non valvular atrial fibrillation—Dabigatran (Pradaxa) and Rivaroxaban (Xarelto). We will also take a look at three studies that compared each individually head to head with warfarin to see how each stacks up.

Apixaban

Apixaban is an additional player to the class of Factor Xa Inhibitors that is currently approved for stroke and systolic embolism prevention in non-valvular atrial fibrillation patients. It works to directly inhibit factor Xa which lowers the production of thrombin reducing the chance of clot formation.[1]

The dosing is 5 mg twice daily unless the patient meets two of the following criteria: $\geq$80 years of age, weighs $\leq$60 kg, or SCr $\geq$1.5 mg/dL. If the patient meets two of the criteria, the recommended dose is 2.5 mg twice daily. Apixaban has not been studied in patients who have a CrCl < 15 mL/min, but the AHA & ASA do not recommend its use in patients with CrCl < 25 mL/min. This medication is not recommended for use in patients who have severe liver disease (Child-Pugh class C). Do not use in patients receiving hemodialysis either.[1]

There are extensive guidelines available for converting to/from Apixaban to/from other anticoagulants. They are available on the Apixaban summary sheet that is in your handout. The key thing to remember when converting to or from Warfarin is that Apixaban affects the INR, so complete coverage is important when switching agents.[1]

Apixaban can be taken with or without food. It is contraindicated in patients who have active bleeding or who have had a sensitivity reaction to it. The medication also requires REMS because of the danger of ending therapy without bridging to another anticoagulant. It is affected by strong CYP3A4 and P-glycoprotein inhibitors like ketoconazole, clarithromycin, and ritonavir. If a patient must take both medicines, then the daily dose should be lowered to 2.5 mg twice daily. If they are already a candidate for the low dose due to other criteria, then this medication is not recommended for use.[1,2]

A big concern with Apixaban is that there is really not a solid option for reversal in the event of severe bleeding or overdose. It does not have an antidote and can not be dialyzed. Some options include prothrombin complex concentrate or factor VIIa neither of which has been studied for this purpose. Activated charcoal is also a consideration but only if the medication has been taken 2-6 hours prior to coming to the hospital.[1]

Apixaban can cause hematomas in patients who have received spinal or epidural anesthesia. It needs to be stopped 48 hours prior to a surgical procedure that is moderate or high risk of bleeding but only 24 hours for low risk procedures. When hemostasis is achieved after surgery, it is acceptable to restart therapy. The most common adverse effect is bleeding (5-12%) which is to be expected.[1]

As mentioned earlier, there are a number of medications that can affect Apixaban, so I recommend checking for interactions when a new patient is started on it just to be sure. I will briefly review some of the reactions though like not using other anticoagulants unless following the conversion guidelines to do so. Medications that are P-glycoprotein and CYP3A4 inducers like rifampin, carbamazepine, phenytoin, and St. John's Wort should be completely avoided because they can decrease the concentration levels of Apixaban. CYP3A4 inhibitors were mentioned earlier, and it is recommended to avoid grapefruit juice if possible.[1,2,3]

Routine monitoring of Apixaban is not required which is one thing that makes it such a strong contender against warfarin. It is known that the prothrombin time, INR, and aPTT are lengthened while patients are taking Apixaban. While the prothrombin test is 10-20 times more sensitive to Apixaban, none of these tests are predictable enough to use to monitor the drug's therapeutic level. Anti-FXa assays could be useful in making medical decisions.[1,2,3]

Apixaban is 87% bound to proteins in the body and is metabolized mainly by the liver. The half-life elimination for a 5 mg dose is approximately 12 hours. The onset of action is between 3-4 hours which is a much shorter wait time when compared to warfarin.[1,2]

Dabigatran (Pradaxa) and Rivaroxaban (Xarelto)

Table 1 is a good side by side comparison of Apixaban to the other oral agents that have entered the market in the last couple of years. After we briefly look at the table, we will take a look at each agent up against warfarin in three different head to head trials.[1,2,4,5]

As you will see, some of the differences are as follows: Dabigatran has a different MOA from the other two medications, and Rivaroxaban has several indications in addition to what the others are approved for at this time. Also, some of the contraindications are slightly different among the three. Known reversal agents and processes vary slightly with the biggest differences being that Dabigatran can be somewhat removed by dialysis. REMS is also needed for all of them but Dabigatran. Renal dosing variations are present, and surgery discontinuation times vary also. Conversion guidelines to other anticoagulants vary as well. An example is that the INR needs to be less than 2 when

switching from warfarin to Apixaban or Dabigatran, but the INR needs to be less than three when switching from warfarin to Rivaroxaban.[1,2,4,5]

ARISTOTLE Trial

The first trial I want to take a look at the ARISTOTLE trial to see how Apixaban compares directly with warfarin treatment. This trial was a randomized, double-blinded trial with a median follow up time of 1.8 years. There were over 18,000 patients with AF who had at least one other risk factor for stroke. The study was looking at a primary outcome of ischemic or hemorrhagic stroke or a systemic embolism. The main goal was to evaluate the medication for noninferiority, but it also looked at superiority as a secondary goal. The study also looked at bleeding rates and the death rates for any cause.[6]

Table 2 provides a nice summary of the results from this study. Most of the results in the study were statistically significant in favor of using Apixaban over warfarin. Adverse drug events and rates of discontinuation were very similar in the two groups.[6,7]

Overall the study shows that Apixaban is superior to warfarin for patients with AF. The chances of having a stroke or embolism were lowered by 21%, the chance of major bleeding was lessened by 31%, and risk of death by 11% with apixaban use over warfarin.[6]

RE-LY Trial

The RE-LY trial evaluates the use of Dabigatran compared to warfarin for atrial fibrillation. It was a noninferiority trial with over 18,000 patients involved. The median follow up was 2 years for patients who were blinded to either a 110 mg or 150 mg dose of dabigatran or not blinded to a dose of warfarin. The primary outcome of RE-LY was stroke or systemic embolism. The primary safety outcome was major bleeding.[8]

Table 3 shows the results from this trial. One item of note in this study was that dyspepsia occurred in the warfarin group at a rate of 5.8% while the Dabigatran 110 mg results were 11.8% and the Dabigatran 150 mg results were 11.3% with a P value of $P<0.001$ for both. Also, the rate of discontinuation at 2 years was at 21% for dabigatran patients versus 17% in the warfarin group with a $P<0.001$. There was also a statistically significant higher rate of MI with patients taking Dabigatran 150 mg. They had a 0.74% incidence rate while the warfarin group had a 0.52% rate with $P=0.048$. Overall the study showed both doses of Dabigatran to be non-inferior to warfarin for the primary outcome. The higher dose was also considered superior to warfarin for the primary outcome and the lower dose was superior for major bleeding risk.[7,8]

ROCKET AF Trial

This randomized, double blinded trial sought to compare Rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. Over 14,000 patients were evaluated for the primary outcome of stroke or systemic embolism to see if rivaroxaban was non inferior to warfarin. The primary safety outcome was to evaluate the risk of major and non-major bleeding.[9]

Table 4 shows the data for this trial. Other results included similar numbers for MI and ischemic stroke events, but the hemorrhagic stroke results were different. In patients taking Rivaroxaban, the event rate was 0.26 events per 100 years, and in warfarin patients it was 0.44 events per 100 years giving a P=0.024. Adverse event results showed GI bleeding and epistaxis were more common in the patients taking Rivaroxaban with P<0.001 and P<0.05 respectively. Overall this study did show that Rivaroxaban was not inferior to warfarin for use in non-valvular atrial fibrillation patients. The two study groups were comparable though in major bleeding outcomes although the individual results for intracranial and fatal bleeding showed favor for rivaroxaban.[7,9]

Patient Considerations & Study Limitations

While the studies do show a number of statistically significant results in favor of the three alternative agents, there are some things we do have to consider. Apixaban has results in its favor, but it is dosed twice daily, is pricier than warfarin, has drug interactions, and has renal dosing adjustments that make it an unlikely choice for some patients.[7]

With Dabigatran, you do have twice daily dosing, a higher cost, P-gp interactions, and renal dosing restrictions. In patients over 75 years of age, Dabigatran showed higher rates of major bleeding and GI bleeding.[7]

Rivaroxaban has its drawbacks as well. It is more costly than warfarin, needs to be avoided in those patients with severe renal or liver impairment, has drug interaction concerns, and has to be taken with a meal if taking over 15 mg per dose. The higher rates of GI bleeding are a definite concern for patients too.[5,7]

All three of these medications lack a really sound reversal agent although Dabigatran can be dialyzed to some extent. Although lack of monitoring is a good thing for these agents, it may also be a drawback. For patients on warfarin, the consistent monitoring could be helpful in maintaining higher rates of compliance and for making sure drug levels are adequate. Without the monitoring, we may not really know how well an agent is or isn't working until an adverse event occurs.[7]

The three studies we have discussed have some solid evidence, but as with most studies they have a few limitations that make it hard to compare the studies to each other to try to determine the best of the three agents. The compliance rates to warfarin in all three studies were not great—RE-LY 64%, ROCKET AF 55%, and ARISTOTLE 62%. This could lead to a change in the results in favor of warfarin if more people were therapeutic throughout the study. Each study had different average $CHADS_2$ scores also with RE-LY and ARISTOTLE being an average of 2.1 and ROCKET AF having an average score of 3.48. The studies were slightly different designs also which makes it more challenging to compare them. The primary safety outcome also varied slightly in the trials.[6,8,9,10]

Conclusion

While we can loosely compare the agents to each other based on their individual study results, it is impossible to make a direct comparison without actual study results to back them up. Since that is most likely not going to happen any time soon, we have to ask ourselves certain questions when looking at a patient and determining if any of these three agents is appropriate. Do they have renal impairment? How is their liver function? What is their age, weight, and SCr for Apixaban? What other medications are they taking? Are we treating non-valvular atrial fibrillation or something else? Is there a risk of MI already? Does the patient already have dyspepsia issues? Is the patient going to realistically take this medication twice daily? Once we answer these questions, we will then have to use our judgment to make the most sound therapeutic choice we can to help create the most favorable outcomes for our patients.

References

1. Lexi-Comp Website. "Apixaban." http://online.lexi.com.cuhsl.creighton.edu/lco/action/doc/retrieve/docid/patch_f/3804162. Accessed February 20, 2013.

2. Clinical Pharmacology Website. "Apixaban." http://www.clinicalpharmacology-ip.com.cuhsl.creighton.edu/Forms/drugoptions.aspx?cpnum=3795&n=Apixaban&t=0. Accessed February 22, 22, 2013.

3. Nutescu E. Apixaban: A novel oral inhibitor of factor Xa. *Am J Health-Syst Pharm*. 2012; 69: 1113-1126.

4. Lexi-Comp Website. "Dabigatran." http://online.lexi.com.cuhsl.creighton.edu/lco/action/doc/retrieve/docid/patch_f/1200582#f_pharmacology-and-pharmacokinetics. Accessed February 22, 2013.

5. Lexi-Comp Website. "Xarelto." http://online.lexi.com.cuhsl.creighton.edu/lco/action/doc/retrieve/docid/patch_f/1275239. Accessed February 22, 2013.

6. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. *NEJM*. 2011; 365: 981-992.

7. Hollands JM, Gowan M, Riney JN, et al. Role of New Drugs for Management of Atrial Fibrillation. *The Annals of Pharmacotherapy*. 2012; 46:1656-1670.

8. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *NEJM*. 2009; 361: 1139-1151

9. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *NEJM*. 2011; 365: 883-891.

10. Xu B, Whitbourn R. Novel Anticoagulants for Non-valvular Atrial Fibrillation. *Heart, Lung, and Circulation*. 2012; 21: 463-467.