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# Differentiation Between Apixaban and Rivaroxaban and the Potential Healthcare Impact of a Seemingly Simple Marketing Change

## The Power of Science and the Voice of the People

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# Outline

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# Background

- In 2021 CVS Caremark made the decision to have only rivaroxaban, one of the frequently prescribed DOACs (*D*irect Acting *O*ral *A*nti*C*oagulant), available to customers on the formulary (removing the access of the patients to other available DOACs)
    - Can have serious healthcare consequences
- In December 2021, a letter was written by the President of American Society of Hematology (ASH)
    - Objected to this unilateral decision & explained how this DOAC is a treatment of choice to certain patients (those who have greater renal insufficiency)

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December 22, 2021

Troyen Brennan, MD, Chief Medical Officer
CVS Health
One CVS Drive
Woonsocket, RI 02895

Dear Dr. Brennan,

I am writing on behalf of the American Society of Hematology (ASH) to express concern about the recent decision by CVS to limit some commercial health plan formularies to only one direct oral anticoagulant (DOAC), Xarelto (rivaroxaban), and warfarin. ASH is gravely concerned about the impact this will have on patients and urges CVS to reconsider moving forward with this policy change.

ASH represents more than 18,000 clinicians and scientists worldwide who are committed to the study and treatment of blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sickle cell anemia, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy.

As you know, DOACs are used to treat acute venous thromboembolism (VTE), a common and serious blood clotting condition that includes both deep-vein thrombosis (DVT) and pulmonary embolism (PE). CVS's decision to limit formularies to one DOAC will force beneficiaries to switch their anticoagulation therapy. In many instances, however, it is more clinically appropriate and safer to treat a patient with apixaban rather than rivaroxaban. For example, apixaban can be given to patients with a greater degree of renal insufficiency.[1] The use of rivaroxaban in patients with creatinine clearance <15 mL/min is contraindicated. However, product labeling for apixaban permits its use in patients with end-stage kidney disease and emerging data indicate that apixaban is an option in these patients.

Additionally, apixaban has a lower bleed risk than rivaroxaban. In a meta-analysis directly comparing apixaban to rivaroxaban in patients with acute VTE, both major and minor bleeding events were significantly higher in the rivaroxaban group. The paper also notes that previous studies have shown apixaban to be safer in patients with advanced age, baseline active cancer, chronic kidney disease, and provoked VTE.[2] The increasing use of anti-platelet therapy in patients on DOACs due to the expanding use of cardiovascular procedures particularly in the aging population increases further the risk of bleeding if apixaban is replaced by rivaroxaban especially if there is concurrent renal insufficiency. Rivaroxaban has also consistently demonstrated higher rates of gynecologic bleeding compared to other DOACs and apixaban is a preferred alternative in this patient population. And in a number of studies, especially in older patients, rivaroxaban

# Materials and Methods

- Several articles and literature were used to conduct this study
- Three aims of the study
  - Examine the similarities and differences between apixaban and rivaroxaban as anticoagulant drugs
  - Demonstrate why apixaban, compared to rivaroxaban, is a more optimal anticoagulant choice in certain patient population
  - Discuss the original marketing decision of CVS and its reversal of this decision
- To add insight into the reversal of the decision, we interviewed Ms. Beth Waldron, a patient advocate who was able to help reverse CVS's decision

# Differentiation Between Apixaban and Rivaroxaban

## Similarities:

| | |
|---|---|
| Mechanism of Action | Oral, direct, and highly selective inhibitor of free and clot-bound factor Xa and prothrombinase activity, which inhibits clot growth and initiates the decrease of thrombin generation and thrombus development, thus inhibiting platelet aggregation.[1] |
| Half-life | Apixaban: 8-11 hours[4]<br>Rivaroxaban: 5-9 hours[8] |
| Metabolism | Use CYP3A4 system (additionally, apixaban's other metabolic pathways are hydroxylation and sulfation of hydroxylated O-demethyl apixaban, and rivaroxaban also uses CYP2J2-, CYP- independent mechanisms)[4] |
| Reversal Agents | Andexanet alfa (a factor Xa decoy that binds to the factor Xa inhibitors in the blood, which prevents them from obstructing FXa)[1] |

# Differentiation Between Apixaban and Rivaroxaban (cont.)

**Differences:**

| | Apixaban | Rivaroxaban |
|---|---|---|
| Onset of Action | 1-2 hours [2] | 2-4 hours[4] |
| Peak levels in Blood | 16-108 ng/ml (after 2.5mg dose)[3] | 90-190 ng/ml (after 10mg dose)[3] |
| Dosage | Twice daily[7] | Once daily[7] |
| Absorption | Absorbed primarily in small intestine and decreases progressively throughout gastrointestinal act[1] | Absorbed primarily in stomach[11] |
| Distribution | Limited extravascular tissue distribution; distributes primarily into extracellular fluid; volume of distribution is about 21 L[1] | Low-to-moderate affinity to peripheral tissues; volume of distribution is about 50 L[8] |

# Differentiation Between Apixaban and Rivaroxaban (cont.)

## Differences (cont.):

| | **Apixaban** | **Rivaroxaban** |
|---|---|---|
| Excretion | Through urine by kidneys (limited), direct intestinal excretion, hepatic metabolism by liver (75%)[5] | Through urine by kidneys (account for 66% of excretion), fecal matter by intestinal tract, hepatic metabolism by liver through CYP3A4 isozyme[4] |
| Side Effects | Bleeding[4] | Bleeding, anemia, nausea, increased gamma-glutamyl transferase (GGT), as well as an increase in other transferases[4] |

# Differentiation Between Apixaban and Rivaroxaban (cont.)

## Food Effect

- High-fat, high-calorie meals, or medications that change gastric pH don't seem to affect on absorption of rivaroxaban or apixaban
- Rivaroxaban can be taken with or without food, but it's been shown in tests that in who people who eat, it takes a longer time to reach maximum concentration than in people who fast

## Drug Interactions

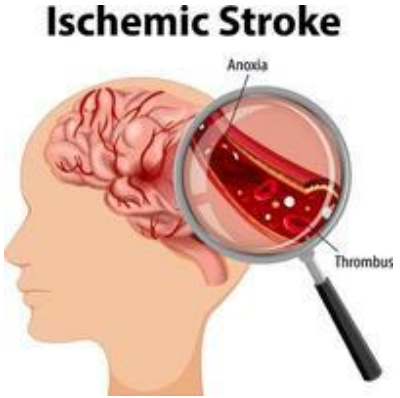
- Rivaroxaban and apixaban react similarly when they interact with CYP3A4 inhibitor and P-gp inhibitor

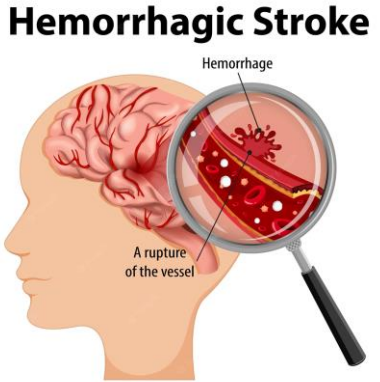
## Efficacy

- Both drugs have an equivalent efficacy in preventing recurrent VTE (recurrent VTE occurred in 1.14% of patients in apixaban group and in 1.35% of patients in rivaroxaban group) in 2019 study but major and minor bleeding occurrences were higher in the rivaroxaban group

# Effect on Certain Patient Populations

- Apixaban is a better choice for patients with increased risk of bleeding, chronic kidney disease (CKD), or end-stage renal disease (ESRD)
  - When a patient has severe renal insufficiency, rivaroxaban will continue to remain in bloodstream
    - Causes anticoagulant to accumulate in the body to levels that cause bleeding
- In a 2021 study of Medicare beneficiaries, incidence of major ischemic or hemorrhagic events was increased for patients 65 years or older with atrial fibrillation
  - Risk of primary outcome (ischemic or hemorrhagic stroke, fatal extracranial bleeding) was increased for those who took rivaroxaban
  - Risk of secondary outcome (non-fatal bleeding) was also increased



# Reversal of CVS's Decision

- When Ms. Beth Waldron first received the letter from CVS, she was shocked and couldn't stand to see the injustice around her, so she decided to take action
- Multifaceted process: physicians, patients, pharmacists, thrombosis non-profits
  - Physicians in ACC, ASH, AHA met directly with CVS to express professional-level concerns
  - Waldron and other patient advocates used social media and news media
    - Very effective; made CVS very concerned about its public image
- This "organic, collective group action" finally made CVS Caremark reverse their decision
  - However, Caremark still hasn't directly notified patients of this reversal (reflection of poor patient communication from CVS)



# Suggestions for Future

- Non-medical switching is a common legal practice but shouldn't happen again
- Professional medical societies need to be more vocal about negative impacts of corporate practice of medicine & importance of patient safety
- Look for ways to get anticoagulants added to Medicare's list of protected drug classes
- Have fail-safe protections in place

# Summary & Conclusions

- The safety profiles of apixaban and rivaroxaban indicate that there is a lower incidence of brain bleeds in patients treated with apixaban rather than rivaroxaban
  - Causes many physicians to believe that apixaban is a safer anticoagulant
- Apixaban seems to be a better choice than rivaroxaban in patients with increased risk of bleeding & for patients with CKD or ESRD
- Apixaban also appears to be a better choice in patients 65 years or older with atrial fibrillation due to the lower incidence of major ischemic or hemorrhagic events
- Demonstrates that drugs within one class don't share the same pharmacologic profile
  - Until scientifically proven, each drug cannot be used interchangeably with another drug
- CVS Caremark was pressured to reverse their decision due to the strong power of patients' voices through social media, non-profits, and more
- These findings highlight the dangers of non-medical switching as well as the importance of patient advocacy

# Future Plans

- I hope to write an abstract and submit it for the 2023 Experimental Biology meeting
- I also plan on writing a position paper on this topic for *Journal of Clinical and Applied Thrombosis and Hemostasis*

# Acknowledgements


- I would like to thank my mentors Dr. Walenga and Dr. Laddu for helping me throughout my research and answering any questions that I had
- I would also like to thank the Loyola staff, including Dr. Fareed, Dr. Siddiqui, and Dr. Bulent Kantarcioglu

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