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OCEANIC-AF

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Global Thrombosis Forum

in collaboration with

Science Valley Research Institute

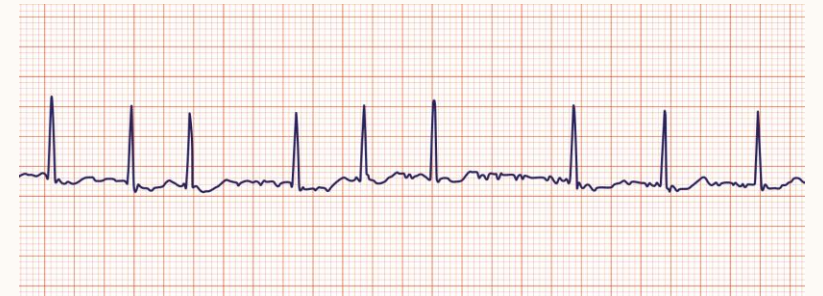
July 21st, 2023

OCEANIC-AF TRIAL

- What is the effect of asundexian on the risk of bleeding vs apixaban in patients with moderate to severe cases of atrial fibrillation?
- This trial is evaluating the efficacy and safety of asundexian in preventing the risk of bleeding and thromboembolic events from occurring compared to a known comparator of apixaban.

BACKGROUND

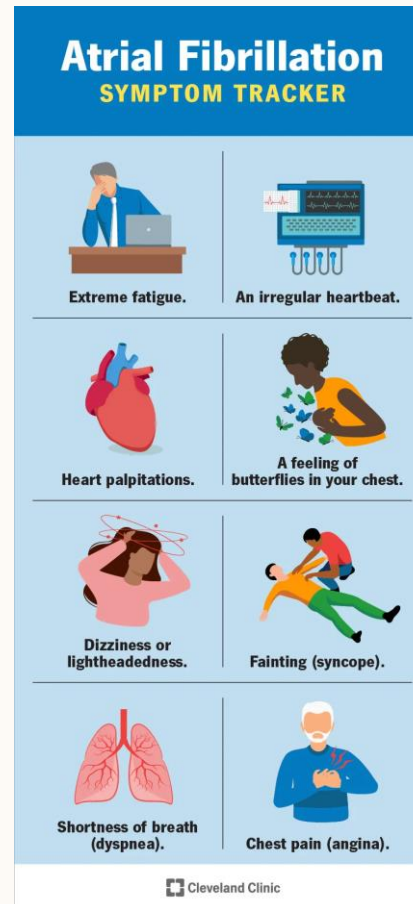
- Atrial fibrillation, (A-Fib) is a heart arrhythmia which is a very fast beating of the heart leading to potential blood clots or thromboembolic events within the heart.
- In atrial fibrillation the heart's atria tend to beat randomly and are not synced with the ventricles.
- Causes blood leakage within the heart (leads to blood clots).
- Usually, there are no symptoms of A-Fib, but shortness of breath and palpitations can be signs.



EPIDEMIOLOGY

- 2.2% of Brazilians receiving an ECG were deemed to have A-Fib
- It is steadily increasing by 0.1%, on average, every year
- The chance to have A-Fib increases almost 7 times from ages 60-69 to 70-79
- The mortality rate is about 50,000 patients every year, which is also steadily increasing.

BURDENS



- Shortness of breath
- Increased risk of stroke, heart failure, and other such types of diseases
- Fatigue
- Feeling of butterflies
- Excessive fainting
- Chest pain

TREATMENTS



- There are many ways to treat A-Fib based on cause.
- Medications that reduce the risk of stroke. (most common)
- Medications that control the Arrhythmias (quite common, amiodarone)
- Electric shock treatment (cardioversion) can also be used to try and shock the heart back into rhythm.
- Fitting a pacemaker to replace the function of the SinoAtrial (SA) node of the heart.
- Celebrities with a pacemaker fitted include Mother Teresa, Stan Lee, and Sir Elton John.

BENEFITS & LIMITATIONS

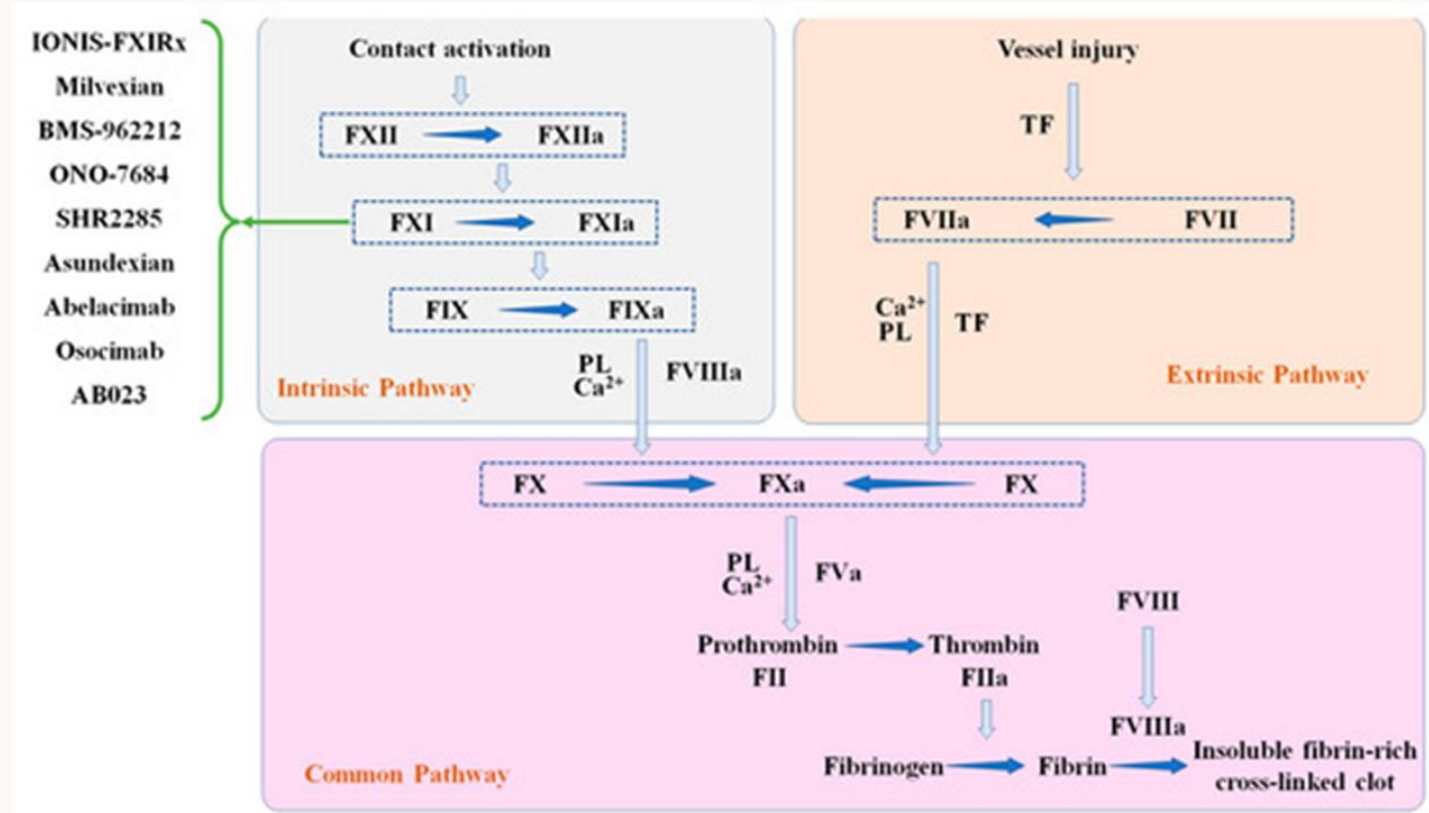


- The benefit of using Factor XIa inhibitors such as asundexian is they have the potential to prevent thromboembolic events from occurring without increasing the risk of bleeding.
- Factor Xa inhibitors (most anticoagulants) reduce the risk of blood clots by thinning the blood, which in turn increasing the risk of bleeding.
- However, Factor XIa inhibitors don't do this, they prevent these thromboembolic events from even occurring by blocking the intrinsic pathway. This way, the extrinsic pathway of the cascade can still occur, allowing a lower risk of bleeding.

PHARMACOLOGY OF ASUNDEXIAN

- Asundexian is a Factor XIa inhibitor which can be administered orally.
- It blocks Factor XIa of the intrinsic pathway, clotting half of the coagulation cascade.
- This results in free cascading of the blood down the extrinsic pathway, for a lower risk of bleeding (compared to Factor Xa inhibitors, blocking both pathways).

PHARMACOLOGY OF ASUNDEXIAN



HOW IS ASUNDEXIAN METABOLIZED?

- Asundexian is a monoclonal antibody which results in little to no renal/liver activity is used when metabolizing Asundexian
- In this case, Asundexian has about 15% of renal elimination
- This way, Asundexian can still be used in patients with kidney failure unlike other anticoagulants

STUDY POPULATION

- Participants with AF at moderate to high risk for future thromboembolic events, qualifying for oral anticoagulant therapy
- Relevant patients include patients with A-Fib needing a reduced risk of strokes occurring, or patients unable to use anticoagulants
- Since asundexian tends to have a reduced bleeding risk compared to apixaban (so far), its target audience could change as time goes on to anybody with a risk of thromboembolic events or strokes, as asundexian prevents these from occurring quite well

INCLUSION CRITERIA

- Patients must be at least 18 years old (by the time of signing the informed consent)
- A-Fib via ECG evidence that cannot be treated with anticoagulants
- CHA₂DS₂-VASc score >3 if male or >4 if female or a score >2 if male or >3 if female if any of the enrichment criteria are met.

EXCLUSION CRITERIA

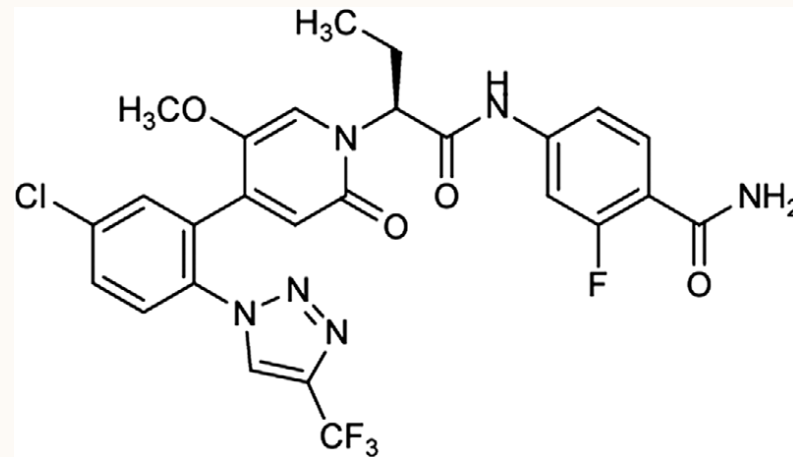
- Age >70
- Previous stroke, ischemic attack, or systemic embolism
- Renal dysfunction with eGFR <50 ml/min within 14 days prior to randomization
- Prior episode of non-traumatic major bleeding
- Current single agent antiplatelet therapy planned to continue for at least 6 months after randomization
- <6 consecutive weeks of treatment with oral anticoagulant prior to randomization

EXCLUSION CRITERIA

- Patients with mechanical heart valve prosthesis (one-way heart valve replacement)
- Moderate to severe mitral stenosis (narrowing of the mitral valve)
- A-Fib due to reversible lifestyle changes (eating less, exercising more, no prolonged sitting)
- Requirement for chronic anticoagulation not for A-Fib (for DVT, or other reasons)

INTERVENTION

- The intervention (drug in this case) being considered in asundexian (BAY2433334).
- It is under consideration for use to prevent thromboembolic events from occurring.



STUDY DESIGN

- It is a randomized, quadruple-blind (participant, care provider, investigator, outcomes assessor), matched pairs designed interventional study in which there are two groups.
- In the experimental asundexian group, participants will receive asundexian once a day, with an apixaban matching placebo twice a day (to mimic the effects of apixaban).
- In the experimental apixaban group, participants will receive 5 mg or 2.5 mg twice a day of apixaban as written on the product label, with an asundexian matching placebo once a day.

MAIN COMPARATOR

- Apixaban is the main comparator with the intervention.
- Since apixaban and other such Factor Xa inhibitors tend to have a high risk of bleeding in patients, it is used as the comparator to easily see the difference in bleeding and ability to prevent thromboembolic events from occurring.
- Apixaban was used instead of other Factor Xa inhibitors due to its lower rates of ischemic strokes and systemic embolisms, on average.

OUTCOMES/ENDPOINTS

- Time to first occurrence of composite of stroke
- Time to first occurrence of systemic embolism
- Time to first occurrence of ISTH major bleeding.
- The study will keep collecting data until a certain number of strokes or embolisms happen in the study.

- All primary and secondary outcomes/endpoints are time-based to reflect the efficacy and safety of asundexian.

IS TIME IMPORTANT?

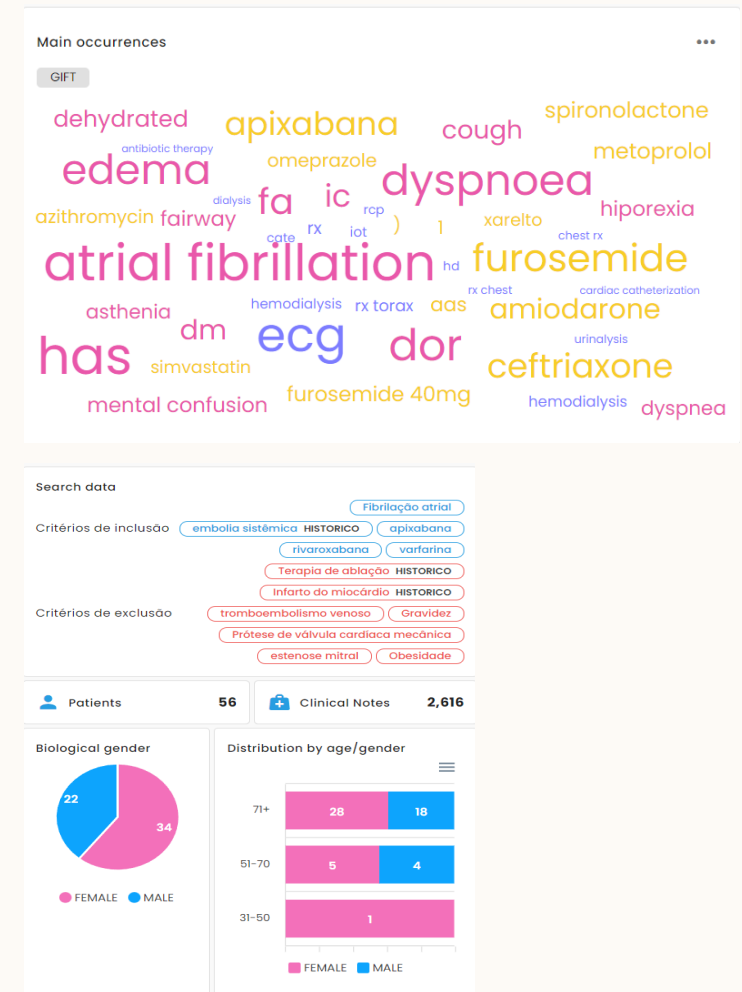
- Yes, time is very important to our search
- The study will last from 9-34 months long in which patients will be taking either asundexian and an apixaban matching placebo, or Apixaban and an Asundexian matching placebo.
- It is very important that the patients follow the protocol and actively take all 3 pills (asundexian once a day and apixaban twice a day) for the duration of the trial to get accurate results.

RECRUITMENT PLAN

- Step 1 – Use AI Tool for Initial Search and Recruitment of patients
- Step 2 – In the hospital physicians (after being informed about the study and are willing to refer patients) can talk to patients
- Using a hospital's EHR/Written Health Records for checking eligible criteria
- Flyers can be posted around the hospital and outpatient settings, given directly to patients, or advertise these flyers digitally or in public.
- Step 3 – Using patient demographics from the AI Tool, search in areas in which patients might be. For example, many people with life threatening diseases tend to pray, or visiting nursing homes.

DEMOGRAPHICS

- There were 22 males and only 34 females.
- There was an average of approximately 46 notes per patient.
- 46 out of the 56 patients found were over the age 70, and all 56 patients actively had atrial fibrillation.
- There were 20-30 patients each on drugs such as furosemide (diuretic), ceftriaxone (antibiotic), metoprolol (blood pressure reduction), amiodarone (anti arrhythmic), and apixaban (DOAC).
- The top procedure by far for these patients was an ECG/EKG, with X-Rays and CT scans coming in a close 2nd and 3rd.
- The most common effects the patients felt were dyspnea, edema, and dehydration.

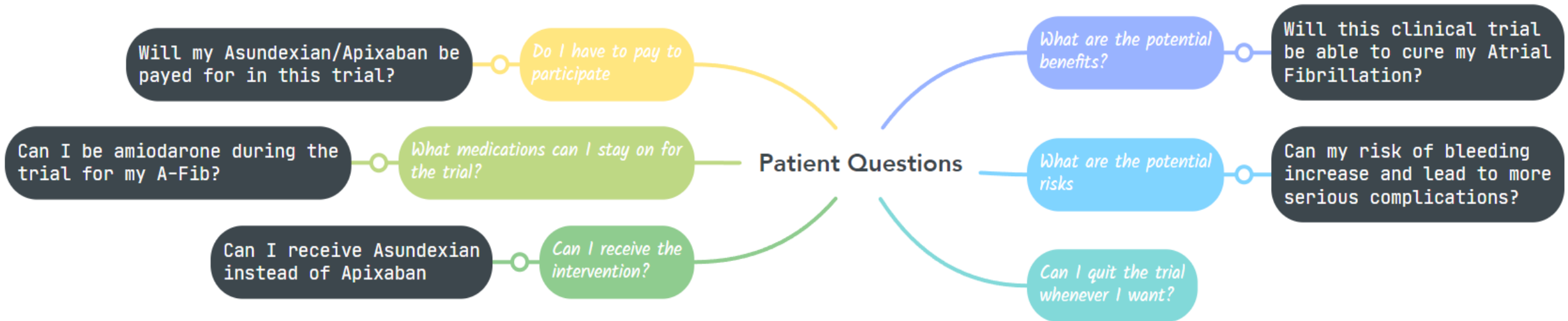


RESEARCH QUESTION

Next steps:

- What is the effect of asundexian on the patient's quality of life vs Apixaban in patients with high risk for, or previous stroke episodes?
- To test asundexian's ability to increase the patient's quality of life compared to known and effective drugs.

COMMON QUESTIONS



INTERNSHIP EXPERIENCE

Dr. Eduardo Ramacciotti and Dr. Camilla Ribeiro planned this internship for us at GTF.

At this internship we:

- Learned about our respective clinical trials at SVRI (OCEANIC-AF and VICTORION-1)
- Practiced presenting our presentations at SVRI to the team and received feedback
- Presented the “Sharing the GTF Experience Presentation” to 3 groups (twice at SVRI, twice at the hospital, and once at Santa Casa De Santos)
- Shadowed Dr. Eduardo Ramacciotti at his outpatient clinics (Patients recovering from ulcers, surgery, varicose veins, PAD, Aneurysms, DVT, VTE, etc.)

INTERNSHIP EXPERIENCE

- Viewed the VICTORION-2 Recruitment and Dosage Process for patients under Dr. Valeria Aguiar (informed consent, drawing of blood, filing paperwork)
- Viewed Surgeries in the OR with Dr. Ramacciotti (3 vascular surgeries, C-Section, rectal surgery, orthopedic knee surgery, umbilical hernia)
- Visited Santa Casa de Santos Hospital (learned about its history, visited the historic medical records archive as well as noted how medical records were stored in containers, visited the resident's library, accompanied doctors to the robotic surgery sector where we saw the latest Da Vinci robot). Our visit was published on the hospital's website -

<https://santacasadesantos.org.br/portal/comunicacao/noticias/estagiarios-norte-americanos-visitam-a-santa-casa-de-santos>)

INTERNSHIP EXPERIENCE

- We really enjoyed every aspect of this internship, especially viewing the various surgeries under Dr. Ramacciotti and sharing the GTF experience with everyone, and the time it took to get GCP Certified which can be used in our future.
- In the future, I would like to continue the learning experience with viewing different surgeries, actively participated in the recruitment process of patients into our clinical trials, and even make the internship a couple weeks longer to enhance our experience.

PICTURES



SURGERY CENTER

After the surgery



SANTA CASA PICTURE

Group picture



SVRI PRESENTATION

After the presentation on
the final day



ROBOTIC SURGERY

At Santa Casa de Santos
hospital

ACKNOWLEDGEMENTS

- Ultimately, this internship was very thoughtfully planned and a huge learning experience for us, and we are so thankful for this opportunity.
- We would like to take this time to thank the GTF Board of Directors, Dr. Ramacciotti, Ms. Camilla Leandro, and the rest of the people who took time out of their day to help us on this journey.
- We had a lot of fun and once again, are so thankful for each person who went out of their way to help us.

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