

**UNIVERSITY OF CALGARY**

**CONSENT TO PARTICIPATE IN RESEARCH**

TITLE:Blinded Randomized trial of Anticoagulation to prevent Ischemic stroke and Neurocognitive impairment in Atrial Fibrillation: BRAIN AF

**SPONSOR:**  **Dr. Léna Rivard / Montreal Heart Institute**

**FUNDING: Stroke Prevention Intervention Network (C-SPIN)**

**Bayer Global**

**Montreal Heart Institute Foundation**

**Hewitt Foundation**

**CIHR**

**INVESTIGATOR:** Local Principal Investigator: Stephen Wilton, M.D. (403-210-7102)

Local Co-Investigators: George Veenhuyzen, M.D. Derek Exner M.D.

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Katherine Kavanagh M.D.

**BACKGROUND/INTRODUCTION:** Dr. Stephen Wilton andassociates from the Cumming School of Medicine and Libin Cardiovascular Institute at the University of Calgary are conducting a research study.

This consent form is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something described here, or information not included here, please ask. Take the time to read this carefully and to understand any accompanying information. You will receive a copy of this form for your records.

You were identified as a possible participant in this study because you have been diagnosed with atrial fibrillation (AF) and you have a low risk of stroke.

Atrial fibrillation (AF) is an abnormal heart rhythm characterized by irregular and rapid heartbeats of the upper part in of your heart (the atrial chambers). AF is associated with an increased risk of stroke and an increased risk of impairment of one or more brain functions, such as memory, understanding, reasoning and attention.

The risk of blood clots and brain function impairments varies from one individual to another depending on the presence or absence of other factors such as diabetes, hypertension and other medical history. This risk varies from low to a higher risk.

The recommended treatment for patients with AF and a *moderate* *to high* risk of stroke is the use of anticoagulants, such as Warfarin, Rivaroxiban, Apixaban, Edoxaban, or Dabigitran. According to Canadian guidelines, patients with AF and a *low* risk of stroke are recommended no treatment, unless they have other blood vessel conditions known as vascular disease. In this case, low dose Aspirin® is recommended.

**WHY IS THIS STUDY BEING DONE?**

Several studies support a link between AF and tiny clots travelling to the brain causing unnoticed decreased blood flow and a decline in thinking functions.

We believe that blood thinners could decrease the rate of stroke and silent brain function impairment, even in people who are not currently recommended to receive them.

The main objective of this study is to evaluate safety and effectiveness of rivaroxaban (anticoagulant) compared to standard of care [placebo for subjects without vascular disease or Aspirin® for subjects with vascular disease] in reducing stroke and cognitive deficits in people with atrial fibrillation and a low risk of stroke. A reduced dose of rivaroxaban 15 mg per day will be used in this study.

# HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

In the initial phase of the study, 505 subjects have been enrolled in 42 centers in Canada.

Now in this phase (phase II), about 919 additional people, for a total of approximately 1424, from different centers across Canada and France will participate in the study. *50* participants are expected to be enrolled at the *University of Calgary.*  The expected study duration will be to 3 to 7 years, depending on when you joined the study.

# WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

If you are eligible to participate in this study, you will be randomly assigned (like a coin toss) to

to one of the two groups of treatment:

* **Rivaroxaban**
* **Usual care: Aspirin** for patients with vascular disease**, placebo** for all others

The BRAIN-AF study is a double-blind study, meaning that neither you nor the research team know which treatment you receive. However, in an emergency, if it is required, this information can be obtained by the study doctor.

The study drugs as well as instructions on how to take them will be given to you by the research team. We will ask you to take the study medication once daily at the same time and with a meal, for the duration of your follow-up in the study.

The study will consist of visits every 6 months, either in clinic or by telephone/video-conferencing, up to 14 visits in total. Video conferencing will be done with the University of Calgary ZOOM account and require a password for entry to ensure your privacy and security. ZOOM visits will be recorded only locally. These visits will take 15-60 minutes of your time.

These visits will include:

* Medical history and brief physical exam
* Blood samples at some visits and a urine or blood sample for pregnancy if appropriate
* ECG
* Questionnaires about your quality of life and thinking
* Questions regarding side effects of study medications and changes in other medications
* Questions about the atrial fibrillation
* Return of study drug bottles and resupply

As a subject participating in a research project, you will have certain responsibilities which are as follows:

* Avoid participating simultaneously in several research projects;
* Keep the study drugs out of reach of children;
* Tell your study doctor about all medicines you are taking, including prescription and non- prescription drugs and natural products;
* Tell your study doctor about all medical problems, doctor visits, hospital visits and medical procedures that you had have during your participation in the study.
* Inform as soon as possible your study doctor if you need to cancel an appointment. A new appointment will be scheduled;
* At the beginning of the study, we will give you an information card with details of the study and how to contact your doctor in case of emergency. You should always carry this card with you during the study;
* Do not take the following drugs
  + Azoles antifungal (ex. ketoconazole)
  + Inhibitors of HIV protease (ex. ritaronavir)

**WHAT WILL HAPPEN WHEN I AM FINISHED THE FOLLOW-UP PERIOD?**

At your final visit your study doctor will discuss the options and treatments available for your condition and what further follow-up is recommended.

# HOW LONG WILL I BE IN THIS STUDY?

The expected study duration will be to 3 to 7 years, depending on when you joined the study.

**WHAT ARE THE RISKS?**

There are risks with this, or any study. To give you the most complete information available, we have listed many possible risks, which may appear alarming. It is essential you have the chance to think about these risks before you choose to participate. There may be risks in participating in this study that we do not know about yet.

Rivaroxaban and Aspirin® (acetylsalicylic acid) are drugs already commonly used and are approved by Health Canada and the Food and Drug Administration (FDA) of the United States for use in reducing the risk of stroke in patients with AF. As a result, adverse effects of these drugs are already documented.

**Rivaroxaban**

Rivaroxaban is an anticoagulant drug. It can be associated with an increased risk of bleeding. The adverse events most frequently observed are:

Note this information reflects the bleeding risks associated with a 20mg dose of Rivaroxiban, (higher than is being used in this study).

* Bleeding nose 7.4%
* Bruising 3.0%
* Bleeding gums 3.7%
* Blood in urine or stool 3.1-4.1%
* Blood in secretions 2.5%
* Bleeding in the brain 0.1- <1%
* Bleeding in the joints 0.1- <1%
* Bleeding in the muscle tissue 0.01- < 0.1%

The following side effects are also associated with Rivaroxiban 20mg:

* Diarrhea 5.3%
* Constipation 4.5%
* Anemia 3.1%
* Dizziness 6.9%
* Headaches 4.6%
* Swollen limbs 6.1%
* Stomach aches 1.6%
* Rash- itching 1.6%
* Kidney problems 2.3%
* Nausea, vomiting 2.7%
* Decrease in blood pressure 2.0%
* Reduced physical strength and energy 3.1%
* Back and limb pain 2.7%
* Increase heart rate, dry mouth, general discomfort 0.1-1%
* Allergic reactions and skin reactions (rashes), loss of consciousness (fainting), urticaria (hives), localized swelling, jaundice 0.1-1%
* Liver function disorders .001-.01%

A**spirin® (acetylsalicylic acid)**

Aspirin® (acetylsalicylic acid) is a medication that inhibits the platelets in the blood (blood cells that help the blood clot) and is used as standard treatment for vascular disease.

The risk of bleeding may be increased for those taking drugs that also prevent blood clotting, at the same time (including drugs such as clopidogrel or ticlopidine and other drugs used for pain relief). For your security, you are asked to report all medications and herbal products you are taking.

**COVID 19 Related Risks:**

As some of visits for this study must be done in person to allow for tests and procedures, there is an added risk of you being exposed to COVID 19 from other people within the facility or by use of public transit to attend your appointment. We have several measures in place to reduce this risk as much as possible including screening each patient who attends our facility, use of PPE for all staff and patients, restrictions on the number of people allowed within the space, enhanced general cleaning procedures and sanitization of any space a patient occupies immediately following their visit.

**General risks:**

Blood samples for laboratory analysis may cause a mild swelling, bruising/bleeding at the puncture site and/or fainting associated with the blood draw procedure. Blood sampling rarely causes infection.

ECGs are routine procedures in clinical practice, however some minor skin irritation is possible at the site of the electrode adhesive.

**Inconveniences:**

The inconveniences of participating in this project relate to the time spent attending visits and to completing the questionnaires and testing.

The quality of life questionnaires and tests are not intended to diagnose a particular condition. However, it is possible that some questions may create discomfort. You are invited to discuss the situation with the study staff. If appropriate, they may refer you to appropriate resources. You may decline any testing which makes you uncomfortable.

**ARE THERE ANY REPRODUCTIVE RISKS?**

It is not known whether rivaroxaban and Aspirin® causes side effects to pregnant women, to an unborn child, or to children of breastfeeding women. Because of these unknown risks, if you are pregnant or trying to become pregnant you cannot participate in the study. Similarly, if you are breastfeeding a child, you cannot participate in the study.

Women of childbearing potential will be asked to undergo a urine pregnancy test before their participation in this project and this test must be negative.

You should not become pregnant during treatment study. The women participating in this research project and could become pregnant and are still ovulating must definitely use one of the following methods of effective birth control throughout the study: male or female condoms, spermicide, sponge, foams, jellies, diaphragm, intrauterine device (IUD) or oral contraceptive.

Women who have not menstruated for the past 2 years are considered post-menopausal in order to participle in the study without using contraception to prevent a pregnancy or to be surgically sterile.

If, however, you become pregnant during your participation in this project, you should stop taking the study medication and contact the study doctor to discuss with him the various follow-up measures to be taken immediately. With your permission, information about your pregnancy to term will be collected.

**WILL I BENEFIT IF I TAKE PART?**

Although participation in this study may be of no benefit to you personally, it is hoped that what

is learned here will be of future benefit to others suffering from AF.

**ALTERNATIVES TO PARTICIPATION:**

There are several medications to reduce the risk of blood clots and stroke in patients with atrial fibrillation. These include Aspirin®, warfarin (Coumadin), dabigatran (Pradaxa), rivaroxaban (Xarelto) and apixaban (Eliquis). If you have any questions about the risks and benefits of alternative options you can discuss these with the study doctor. Rivaroxaban and Aspirin are both available without having to participate in the study.

**PROCEDURE IN CASE OF DEATH:**

In case of death, it would be useful for the study team to know about your state of health at the time of your death and the causes of it. You can authorize the study doctor to obtain a copy of your medical records from other health care or long-term care facilities at the end of this form. The information collected will be used only for this research and will remain confidential. The information may be shared with the Sponsor or the funder of the study.

**CAN I STOP BEING IN THE STUDY?**

You are free to participate in this study or withdraw from it at any time. You may also refuse to answer any specific questions or withdraw your consent to follow-up visits; you will still receive the standard medical care required by your condition.

If you wish to withdraw please notify the study doctor: Dr. Stephen Wilton: Phone:(403) 210-7102 or (403) 210-6047.

If the event that you decide to stop participating in the study, you will be asked to come back to the clinic to complete the final visit procedures without medication. This is for safety reasons.

If you withdraw or are removed from the project, the information already obtained in this project will be maintained as long as necessary to ensure your safety as well as those of other research subjects and meet regulatory requirements.

# CAN THE RESEARCHERS REMOVE ME FROM THIS STUDY?

The researchers may end your participation in this study for a number of reasons, such as if your safety and welfare are at risk, if you do not follow instructions or if you miss scheduled visits. The researchers or the study sponsor might also decide to stop the study at any time.

**WITHDRAWAL OF STUDY DATA**

If you decide to stop being in the study, or are removed from the study, or the study is stopped, the data collected about you up to that point will remain part of the study because withdrawal of data in clinical trials could bias results.

# WHAT IF RESEARCHERS DISCOVER SOMETHING ABOUT ME?

During the study, the researchers could learn something about you that they didn’t expect. For example, the researchers may find out that you have another medical condition. The researchers will consult with medical experts as needed to evaluate the findings and will then share these results with you. You will be helped with arranging appropriate follow up and care.

**WILL I BE PAID FOR PARTICIPATING, OR DO I HAVE TO PAY FOR ANYTHING?**

No, you will not be paid to participate in this study. Parking costs for follow-up visits at the Foothills Medical Centre or South Health Campus will be paid.

**WILL MY RECORDS BE KEPT PRIVATE?**

During your participation in this study, the research team will collect your health information and store it in your research file. Only information needed for the study will be collected.

All information collected will remain confidential to the limits provided by the law. To protect your identity and confidentiality, you will be identified only by a code number. All data regarding your identity will only be kept at the University of Calgary under the responsibility of Dr. Stephen Wilton.

The study doctor will share the anonymous data collected with the Montreal Health Innovations Coordinating Centre (MHICC) and the research results will be communicated to the sponsor.

The data itself or combined with data from other projects can be shared with the Canadian regulatory agencies (Health Canada) or other countries. This transfer of information means that your data could be transmitted to other countries than Canada. However, the coordination centre will respect the applicable rules of confidentiality in effect in Quebec and Canada, regardless of the country. This data will be kept in a secure area for 25 years by the Sponsor.

The data may be published in medical journals or shared during scientific discussions, but it will not be possible to identify you.

For the purpose of monitoring, control, safety and security it is possible that representatives from regulatory agencies authorities, in Canada or in other countries, such as Health Canada, as well as by representatives of the sponsor, the institution, or the Research Ethics Board will consult your study data, as well as your medical record. All these individuals and organizations adhere to a privacy policy.

You have the right to consult your research record in order to verify the information collected, and correct them as appropriate, and, as long as the study doctor or institution holds this information.

# HOW LONG WILL INFORMATION FROM THE STUDY BE KEPT?

Local study records will be stored for 15 years as per the University of Calgary policy.

**IF I SUFFER A RESEARCH-RELATED INJURY, WILL I BE COMPENSATED?**

In the event that you suffer injury as a result of participating in this research, no compensation will be provided to you by The Montreal Heart Institute, the University of Calgary, Alberta Health Services or the Researchers.You still have all your legal rights. Nothing said in this consent form alters your right to seek damages.

# WHO CAN I CONTACT IF I HAVE QUESTIONS ABOUT THIS STUDY?

**The Research Team:**

You may contact Dr. Stephen Wilton at (403) 210-7102 or 403-210-6047 with any questions or concerns about the research or your participation in this study.

**Conjoint Health Research Ethics Board (CHREB):**

If you have any questions concerning your rights as a possible participant in this research, please contact the Chair, Conjoint Health Research Ethics Board, University of Calgary at 403-220-7990.

**Public Information about this Study:**

ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

# HOW CAN I FIND OUT ABOUT THE STUDY RESULTS?

Study participants may contact the study team for information. Study results are also available on the clinicaltrials.gov website mentioned above.

**CONSENT**

I have had an opportunity to ask all the questions about this research project and have received satisfactory answers. I understand that I remain free to withdraw from this project at any time without it affecting my future medical care in any way. I have read or have been read this information and consent form and I understand its content. After consideration, I accept to participate in this research project with the conditions indicated below:

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| --- | --- | --- |
| I authorize the study doctor to inform my family physician about my participation in this project.  Name and address of family physician:  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | I accept | I refuse |

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| --- | --- | --- |
| In the event that the results obtained in this research gave rise to the development of another research project (sub-study or new research arising directly from this project), I agree to be re-contacted to be asked if I am interested to participate in this sub-study or new project. | I accept | I refuse |

|  |  |  |
| --- | --- | --- |
| In the event of my death, I agree that any institution of health care or long term care, including a hospital, nursing home or medical clinic, provide a copy of my medical records to the doctor for this study if requested. This information may be shared with the Sponsor or the funder of the study. | I accept | I refuse |

**SIGNATURES**

**SIGNATURE OF STUDY PARTICIPANT**

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Name of Participant

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Signature of Participant Date

**SIGNATURE OF PERSON OBTAINING CONSENT**

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Name of Person Obtaining Consent Contact Number

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Signature of Person Obtaining Consent Date

**SIGNATURE OF WITNESS**

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Name of Witness

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Signature of Witness Date

The University of Calgary Conjoint Health Research Ethics Board has approved this research study.

A signed copy of this consent form has been given to you to keep for your records and reference.