PRESTIGE-AF

PREVENTION OF STROKE IN INTRACEREBRAL HAEMORRHAGE SURVIVORS WITH ATRIAL FIBRILLATION

Participant Information Sheet and Consent Form

Chief Investigator: Prof Roland Veltkamp

WE INVITE YOU TO TAKE PART IN A RESEARCH STUDY

We are conducting a research study on the best stroke prevention for people with atrial fibrillation (AF) who have recently had a bleed in their brain, called an intracerebral haemorrhage (ICH). This is a trial where half of the participants will take an anticoagulant medication, preventing blood clot formation, and half will not receive an anticoagulant. Clinical trials, like PRESTIGE-AF, are done to gain knowledge of the best treatments to give patients with a medical condition and they help us to improve patient care.

- Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve.
- Please take time to read the following information carefully. Discuss it with friends and relatives if you wish.
- You are free to decide whether to take part in this trial. If you choose not to take part, this will not affect the care you get from your doctors.
- If you do decide to take part, you can withdraw from the trial at any time without being disadvantaged.
- Ask us if there is anything that is not clear or if you would like more information.

BACKGROUND

Atrial fibrillation (AF) is the most common form of irregular heart rhythm. In people with AF, blood clots often form in the heart, which can travel to the brain. Blockage of brain arteries by these clots is a major cause of stroke. This type of stroke is called an ischaemic stroke and approximately 15% of all ischaemic strokes are caused by AF.

People with AF are often prescribed a medication called an anticoagulant, which makes it less likely for blood clots to form and thus can prevent ischaemic strokes. However, anticoagulants also increase the risk of bleeding, so they are not suitable for everyone.

Some people who have AF have had a different type of stroke which is caused by bleeding in the brain, an intracerebral haemorrhage (ICH). These people are at increased risk of suffering both an ischaemic stroke (due to AF) and another ICH. It is not known whether it is best for these people to take an anticoagulant medication or not, as previous research studies did not include this group of people.

We aim to answer the question of whether people with ICH and AF should take an anticoagulant medication or if it is better for them to avoid it.

WHAT IS INVOLVED?

After reading this information sheet and taking time to think and ask questions you will be asked to decide whether you are willing to take part in this study. If you do consent to take part, you will be randomly assigned by a computer to one of 2 treatment groups. Randomisation is done to be sure that the results of the trial cannot be affected by researcher bias, therefore, we will not be able to choose which group you go into. One group will receive a direct oral anticoagulant (DOAC) the other group will not receive an anticoagulant. If you are in the 'no anticoagulant' group, you can take antiplatelet medication such as aspirin, which is also used for ischaemic stroke prevention, if this is recommended by your doctor.

MEDICATION

The direct oral anticoagulants (DOACs) that will be used in this trial are all licenced for use in the United Kingdom and within the European Union (EU) to prevent strokes in people with AF. However, the current licence does not extend to use with people who have had an ICH because it has not been tested in this group with a randomised controlled trial. This is why we are doing this clinical trial. We are using DOACs because previous research trials have shown that people are up to 50% less likely to have complications such as bleeding in the brain with DOACs than with Warfarin (another commonly used anticoagulant).

DOACs work by blocking certain clotting proteins in your blood. There are four medications which are licenced for use in the EU for prevention in people with AF.

- Apixaban
- Dabigatran
- Edoxaban
- Rivaroxaban

If you are randomised to receive a DOAC we will help you to decide which DOAC is right for you. We will give you advice based on factors such as your age and your kidney function, which can affect which drugs are suitable for you and the dose that is recommended.

RISKS AND BENEFITS OF ANTICOAGULANTS

The PRESTIGE-AF Study seeks to clarify how to prevent strokes in patients who have had an ICH and have AF. The strokes that we are trying to prevent, can be haemorrhagic (caused by bleeding) or ischaemic (caused by a blood clot).

ISCHAEMIC STROKE RISK

Blood clots can block blood vessels and stop blood from flowing to organs such as the brain, heart and lungs. Taking an anticoagulant medication helps to prevent blood clots from forming and reduces

your risk of developing a serious condition such as an ischaemic stroke, a heart attack or a pulmonary embolism (blood clot in the lungs).

The overall risk-benefit ratio for taking anticoagulation or not is currently not known for patients with previous ICH and atrial fibrillation. This is why the PRESTIGE-AF Study is being performed. In general, the individual annual risk of suffering an ischaemic stroke can be estimated in patients with atrial fibrillation based on the presence of risk factors. A widely used tool for risk assessment is the CHA2DS2-VAsc score which includes several risk factors including heart failure, hypertension, age, diabetes, stroke or other major cardiovascular diseases. The score can take values from 0 to 9, with higher scores indicating a higher risk. According to this score, the annual risk of an ischaemic stroke is estimated to be in the range of 0% to 15.2%. Men with a CHA2DS2-VAsc score of less than 2 and women with a score of less than 3 are excluded from the trial because their risk of an ischaemic stroke is too low. Please ask your doctor what your estimated annual risk for an ischaemic stroke is. Data from previous studies suggest that anticoagulants reduce the risk of an ischaemic stroke by more than 50% compared to not taking them. However, these studies did not include patients who had previously had a bleed in the brain.

HAEMORRHAGIC STROKE RISK

The risk of having another ICH is much more difficult to predict than ischaemic stroke risk. The annual risk of recurrent brain bleeding in patients who take anticoagulant medication ranges between 2.5% and 8% in observational studies. One of the predictive factors for the risk of having another brain bleed is the location in the brain of the first bleed. Superficial haemorrhages appear to have a 2- to 3- times higher risk of recurrence compared to deep brain bleeds.

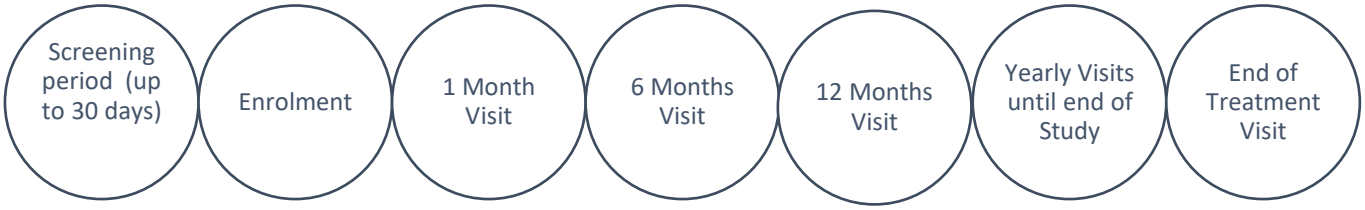
In theory, anticoagulants may increase the risk of having a haemorrhagic stroke but in patients with AF this must be weighed up

against the risk of having an ischaemic stroke. Each stroke can have severe consequences but in terms of survival and disability, haemorrhagic strokes are usually more severe than ischaemic strokes. Therefore, in addition to the estimated individual risk of another ischaemic or haemorrhagic stroke, the severity of the strokes adds to the complexity of decision-making. Without data from large clinical trials such as the PRESTIGE-AF Study, there is uncertainty about how best to manage patients who have both conditions.

OTHER POTENTIAL TREATMENT OPTIONS

Implantation of a left atrial appendage occlusion (LAAO) device may be another option for stroke prevention in patients with atrial fibrillation and a high risk of bleeding who cannot take anticoagulants. LAAO is an invasive heart catheter procedure during which a disk-like device is deployed in the heart that covers the opening of the left atrial appendage to the left atrium. In addition to the procedural risk, there is very limited evidence regarding the long-term efficacy and safety of this procedure in patients with intracerebral haemorrhage. After the LAAO procedure patients have to take dual antiplatelet medication for 1 to 3 months followed by lifelong, single antiplatelet therapy which increases the risk of another bleed. Patients who wish to undergo LAAO are excluded from participation in the PRESTIGE-AF Study.

PARTICIPANT TIMELINE



STUDY PROCEDURES

If you are interested in taking part in the trial you will be given time to ask questions and to discuss it your family or friends if you wish. If you decide to take part you will be asked to sign a consent form. After you have signed the form, you can still decide to stop taking part in the trial at any time, without giving a reason why.

After consent, there is a screening period of up to 30 days for the doctors to do any tests that are needed to check that you are suitable for the trial.

HEALTH TESTS AND MEASUREMENTS

You will have a blood sample taken (3 tubes: approximately 15mls or 3 teaspoons of blood) this will be the same procedure as a standard blood test at your general practitioner (GP) surgery or hospital. We will use this to test:

- Full blood count: to check your general health
- Biochemistry test: to check your liver and kidney function
- Coagulation screen: to check the ability of your blood to clot

If you have had these tests done as part of your normal care you may not need to have them repeated for the trial.

We will do two risk assessments called the CHA2DS2-VASc and HAS-BLED, these are to calculate a risk score for your likelihood of having a

blood clot and your likelihood of bleeding. These will help us to decide if you are suitable to take part in the study.

We will do an Electrocardiogram (ECG) of your heart, which is a simple test that checks your heart rhythm if you haven't already had one. You will also have your weight and height measured.

Part of these assessments is checking your blood pressure because high blood pressure increases the risk of bleeding into the brain. If you decide to take part in the Study your blood pressure will be measured at each study visit. We also recommend that you have your blood pressure regularly checked by your GP or do it at home yourself. If at any time during the study you have high blood pressure, we will advise you to visit your GP for further advice. If you are found to have uncontrolled high blood pressure during screening, you will not be able to take part in the study until it is under control.
If you are a female and have not reached menopause, we will ask you to give a urine sample for us to take a pregnancy test. If you are enrolled into the trial you will need to take regular pregnancy tests if you are randomised to receive a DOAC. If you are pregnant or planning on becoming pregnant during the timeline of the study, you will not be able to take part.

QUESTIONNAIRES AND SCALES

One of the aims of the research is to assess the quality of life of participants, including cognitive and psychological impairment and how this may change over time. To do this, we will perform some assessments and ask you to answer questionnaires. It is possible to decline any question or assessment and still take part in the trial.

- **National Institute of Health Stroke Scale (NIHSS)** – this is a neurological examination, which tests your stroke symptoms, it includes things like testing the strength in your limbs and your speech.

- **Montreal Cognitive Assessment (MoCA)** – a cognitive screening test that assesses memory, attention and visuospatial skills.
- **EQ-5D-3L –** a 5 item health focussed quality of life questionnaire
- **Modified Rankin Scale (mRS)** - a short question-based assessment that measures the level of disability after stroke
- **Hospital Anxiety and Depression Scale (HADS) –** a 14 item self-report questionnaire to measure symptoms of anxiety and depression
- **Barthel Index –** a question led assessment of self-care ability
- **Adherence Questionnaires (MARS and A14)** – two questionnaires with 5 and 14 items to assess medication adherence. Moreover, you will be asked to assess your adherence to treatment regimens in general on a visual scale.

ENROLMENT

If you pass screening and still want to go ahead, you will be enrolled into the trial within 30 days of you signing the consent form. , You may be able to be enrolled on the same day that you consent if you do not need to wait for test results and it has been at least 2 weeks since your ICH. The enrolment will usually occur at the hospital but this can sometimes be at another hospital or place of care if you have been transferred.

The doctor will review all of the screening information to ensure that you are suitable for the trial. Then we will enter your details into a computer which will randomise you and we will tell you which treatment group you have been allocated to.

FOLLOW UP VISITS

You will be seen for follow up visits at the following intervals after your enrolment; 1 month; 6 months; 12 months; 24 months; 36 months and an end of treatment visit. How long you will take part will depend on when you will have been enrolled into the trial. You may only be asked

to take part for 1 year, or it could be up to 3 years. We will be able to tell you this before you decide whether to take part.

Follow up visits will usually take place at the hospital but if you are unable to come in it is sometimes possible to do a remote visit or for someone to visit you at home or where you are staying. During screening and enrolment , we do all the assessments explained above, but it is not necessary to repeat them at every follow-up. The table below shows which tests will be done at each visit.

At each follow-up visit we will also monitor and record:

- **Adverse events:** We will keep a record of any health problems that you may have while you are on the trial.
- **Medication:** We will ask you if you have had any changes in the medication that you take.
- **Medication Adherence:** If you are taking a DOAC you will be asked to fill out a questionnaire about taking your medication and we will count your tablets. If you have missed taking any tablets we will discuss this with you and help you to find ways to remember to take them if you are having difficulty.

Month of Visit							
Visit	**Screening and enrolment**	**1**	**6**	**12**	**24**	**36**	**End of Treatment visit**
Length of visit	**2 hours**	**30 mins**	**30 mins**	**1 hour**	**1 hour**	**1 hour**	**30 mins**
Blood Pressure	•	•	•	•	•	•	•
Blood Test	•	•	•	•	•	•	•
ECG	•						•

Height & Weight	•			•	•	•	
MoCA	•			•	•	•	
EQ-5D-3L	•			•	•	•	
mRS	•	•	•	•	•	•	•
HADS	•			•	•	•	
Barthel Index	•	•	•	•	•	•	
MARS	•	•	•	•	•	•	

TRAVEL COSTS

You will be reimbursed for expenses for travel to visits at the hospital. This will either be the cost of public transport or a taxi if required.

WHAT IF SOMETHING GOES WRONG?

Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (*prestige-af@imperial.ac.uk*) The normal National Health Service mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial College, Research Governance and Integrity Team.

HOW WILL WE USE INFORMATION ABOUT YOU

Imperial College London is the sponsor for this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Imperial College London will keep you personal data for:

- 15 years after the study has finished in relation to data subject consent forms
- 15 years after the study has completed in relation to primary research data.

We will need to use information from you, your medical records, your GP or other healthcare providers for this research project.

This information will include:

- Your name
- Your contact details
- Your NHS Number
- Health information

People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Some of your information will be sent to countries in the European Union. They must follow our rules about keeping your information safe.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

LEGAL BASIS

As a university we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

INTERNATIONAL TRANSFERS

There may be a requirement to transfer information to countries outside the European Economic Area (for example, to a research partner). Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a European Commission (EC) adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient organisation that incorporates EC approved standard contractual clauses that safeguard how your personal data is processed.

SHARING YOUR INFORMATION WITH OTHERS

For the purposes referred to in this privacy notice and relying on the bases for processing as set out above, we will share your personal data with certain third parties.

- Other College employees, agents, contractors and service providers (for example, suppliers of printing and mailing services, email communication services or web services, or suppliers who help us carry out any of the activities described above). Our third party service providers are required to enter into data processing agreements with us. We only permit them to process your personal data for specified purposes and in accordance with our policies.

- This clinical trial is part of a large European Union funded project. We are working with the following research collaborators across Europe who are all specialists in different fields. In order to answer the questions of our research we are all working together and therefore your data will be shared with:

  - University Hospital Würzburg, Germany
  - Julius-Maximilans Universitaet Würzburg, Germany
  - Medizinische Universitaet Graz, Austria
  - Kings College London, UK
  - Fundacio Hospital Universitari Vall d'Hebron- Institut de Recerca, Spain
  - Universite de Bordeaux, France
  - Azienda Ospedaliera di Perugia, Italy
  - Region Nordjylland (North Denmark Region) , Denmark
  - Stroke Alliance for Europe, Belgium
  - Heidelberg University Hospital, Germany
  - University of Liverpool, UK

If you would like to find out more about the PRESTIGE-AF Project and what each partner does there is more information on our website www.prestige-af.org

WHAT ARE YOUR CHOICES ABOUT HOW YOUR INFORMATION IS USED

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

- If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

WHERE CAN YOU FIND OUT MORE ABOUT HOW YOUR INFORMATION IS USED

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by sending an email to hello@prestige-af.org
- www.prestige-af.org/privacy-cookie-policy/

COMPLAINTS

If you wish to raise a complaint on how we have handled your personal data, please contact Imperial College London's Data Protection Officer via:

- email at dpo@imperial.ac.uk
- telephone on 020 7594 3502 and/or
- via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ.

If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO). The ICO does recommend that you seek to resolve matters with the data controller (us) first before involving the regulator.

ABOUT THIS RESEARCH

- We are recruiting patients in several countries across Europe including the UK, France, Germany, Austria, Spain and Italy.
- There are around 70 different hospitals running the trial in Europe, of which about 15 are in the UK.
- We plan to enrol 654 patients into the trial.

FUNDER

A group of international researchers formed the PRESTIGE AF consortium, which applied for research funding. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 754517.

ETHICAL REVIEW

This research was designed and reviewed by a consortium of experts within the field. There are several monitoring boards in place that will continue to review the trial throughout, to ensure the safety of participants.

This research has been reviewed and approved by the London Surrey Borders Research Ethics Committee and the Medicines and Healthcare Products Regulatory Agency. The Health Research Authority has approved this research to be conducted within the UK National Health Service.

FURTHER INFORMATION

It is important that you have enough information to decide whether to take part. If you have any questions, please contact the study team: *prestige-af@imperial.ac.uk*

Thank you for taking the time to read this information.

CONSENT FORM

Principal Investigator:

Participant ID:

	Please initial box
I confirm that I have read this information sheet and I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
I understand that relevant sections of my medical notes and data collected during the study, may be looked at by responsible individuals from the NHS Trust or from regulatory authorities where it is relevant to my taking part in this research.	☐
I give permission for these individuals to access my records that are relevant to this research.	☐
I give / do not give (delete as applicable) consent for information collected about me to be used to support other research in the future, including those outside of the EEA.	☐
I agree to my General Practitioner being informed of my participation in the study and consent to any necessary exchange of information about me between my GP and the research team.	☐

I understand that the information held and maintained by (*insert NHS Trust*) and other UK NHS bodies may be used to help contact me or provide information about my health status. ☐

I consent to take part in the above study ☐

Name of Participant	Date	Signature
Name of Investigator taking consent	Date	Signature
Name of Witness (If oral consent given)	Date	Signature

When completed: 1 for Participant, 1 for investigator site file, 1 to be kept in medical notes