PRESTIGE-AF

PREVENTION OF STROKE IN INTRACEREBRAL HAEMORRHAGE SURVIVORS WITH ATRIAL FIBRILLATION

Participant Information Sheet

Principle Investigator: *(information provided by site)*

WE INVITE YOU TO TAKE PART IN A RESEARCH STUDY

We are conducting a research study on the best stroke prevention in people with atrial fibrillation (AF) who have recently had a bleeding in their brain, also 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. In fact, 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 bleeding complications 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

POTENTIAL BENEFIT AND RISK OF TAKING AN ANTICOAGULANT

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 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). However, a

blood clot forming is a natural process where a seal is created by the blood to stop bleeding from wounds. The main side effect of preventing this process is that you may bleed more easily. This can cause problems such as passing blood in your urine or faeces, bruising, nosebleeds or in serious cases internal bleeding in the brain or other organs. For people who are at increased risk of blood clots, like patients with AF, the benefit of taking anticoagulants will usually outweigh the risk of excessive bleeding.

The overall risk-benefit ratio for each treatment strategy studied in the trial – anticoagulation (intervention) versus no anticoagulation (control) - is currently not known for patients with previous brain bleedings 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 disease. 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 feel free to ask your treating physician 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 no anticoagulation. However, these studies did not include patients with a previous brain bleeding.

The risk of another brain bleeding after a previous brain bleeding is much more difficult to predict. The annual risk of a recurrent brain bleeding in patients who take anticoagulant medication ranges between 2.5% and 8% in previous observational studies. One of the predictive factors for the risk of another brain bleeding is the location of the bleeding in the brain. Superficial haemorrhages appear to have a 2 to 3-fold higher risk of a recurrent brain bleeding compared to deep bleedings.

The PRESTIGE-AF Study seeks to clarify the best stroke prevention in patients with a previous brain bleeding and AF. Recurrent strokes can be haemorrhagic (that is another brain bleeding) or ischaemic. Each stroke can have severe consequences but in terms of survival and disability, haemorrhagic strokes are usually more severe than ischaemic strokes. In addition to the estimated individual risks of another ischaemic or haemorrhagic stroke, the severity of the strokes adds to the complexity of decision-making. In the absence of data from a large clinical trial such as the PRESTIGE-AF trial, uncertainty about the best management in patients with brain bleedings and atrial fibrillation will prevail.

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 single antiplatelet therapy lifelong which increases the risk of another bleeding. Patients who wish to undergo LAAO are excluded from participation in the PRESTIGE-AF Study.

PARTICIPANT TIMELINE

SCREENING VISIT

If you decide to take part in the trial, you will come to see us at (*Insert Hospital*) for a screening visit. You will be given time to ask questions and if you want to take part you will be asked to sign a consent form. After you have signed the form, you can still decide to stop your participation at any time, even without giving a reason why.

Once you have consented, we will do the following tests and assessments to ensure you are suitable to take part in the trial. 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 your bloods ability to clot

If you have had these tests done within the last 7 days, you will 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. 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 to 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.

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 pregnant or planning on become pregnant during the timeline of the study, you will not be able to take part. If you are enrolled into the trial you will need to take regular pregnancy tests if you are randomised to receive a DOAC.

BASELINE VISIT

On the day of your baseline visit we will ask you some questions to check that nothing has changed since your screening visit. Your baseline visit will be within 30 days of your screening visit, you may be

able to have your screening and baseline visit on the same day if you do not need to wait for test results.

We will enter your details into a computer which will randomise you and then we will tell you which treatment group you have been allocated to.

MEDICATION

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.

You will be given instructions on how to take the medication and we will give you the medication to take home with you that day.

BASELINE HEALTH TESTS AND MEASUREMENTS

You will have your blood pressure and heart rate checked and we will do an Electrocardiogram (ECG) of your heart, which is a simple test that checks your heart rhythm. You will also have your weight and height measured.

BASELINE 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 which 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 which measures 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.

MEDICAL RECORDS

If you decide to take part in the trial, you will be agreeing to give us access to your medical records. After you baseline visit we will collect data from your records such as, your medical history, AF diagnosis, details of your ICH and the treatment you have received. We will also request an pseudonymised (see below) copy of your brain scan, from when you were admitted to hospital with your ICH and any other relevant brain scans since. During the trial we will collect any relevant information from your medical records at the hospital, or from your GP. This is necessary to ensure that we can record details of any health problems that you may have during the trial.

All data that we collect about you will be pseudonymised and your information will be treated as confidential. Pseudonymisation means that we will give you a participant ID which will be used to identify you and all personal details about you will removed from the data we collect. We will keep a log of everyone and their code so that we can decode who each participant is to contact them when needed.

FOLLOW UP VISITS

You will be seen for follow up visits at the following intervals after your baseline visit; 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.

At the baseline visit 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.

If you are randomised to take a DOAC there are some additional tests:

Medication Adherence: 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	**Baseline**	**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 & Heart Rate	•	•	•	•	•	•	•
Blood Test	•	•	•	•	•	•	•
ECG	•						•
Height & Weight	•			•	•	•	
MoCA	•			•	•	•	
EQ-5D-3L	•			•	•	•	
mRS	•	•	•	•	•	•	•
HADS	•			•	•	•	
Barthel Index	•	•	•	•	•	•	
MARS	•	•	•	•	•	•	

COMPENSATION

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

CONDUCT AND COORDINATION

Imperial College London (ICL) holds insurance policies which apply to this study. If you experience serious and enduring harm or injury because of taking part in this study, you may be eligible to claim compensation without having to prove that ICL 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 this study then you should immediately inform the Principle Investigator.

The National Health Service complaints mechanisms are also available to you. Patient Advice and Liaison Service (PALS) is an independent service available to patients and relatives who can listen to your concerns and help sort out any problems on your behalf. Contact them on *(information provided by site)*.

CONFIDENTIALITY

Imperial College London is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake 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 identifiable information about you for 10 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already

obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information [Insert Local Principle investigator contact details].

[insert NHS site name] will collect information from you and your medical records for this research study in accordance with our instructions.

[insert NHS site name] will keep your name, NHS number and contact details confidential and will not pass this information to Imperial College London. [insert NHS site name] will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from Imperial College London and its delegates, as well as regulatory organisations may look at your medical and research records to check the accuracy of the research study. Imperial College London will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

[insert NHS site name] will keep identifiable information about you from this study for <insert number based on local policy> years after the study has finished.

DATA SHARING

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or

abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

This trial is being sponsored and is being run by Imperial College London. However, there are 12 other European Partner Organisations in the Prestige AF Consortium with whom we will be sharing the pseudonymised results of this trial. These organisations are other Universities and Hospitals with specialist knowledge in different areas who will assist in the running of the trial and the analysis and publishing of the data. The Partner Organisations are:

- University Hospital Würzburg, Germany
- Julius-Maximilans Universitaet Würzburg, Germany
- Medizinische Universitaet Graz, Austria
- The University of Birmingham, UK
- 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

The aim of this research is to improve patient care and to help us do that we will ask for you to consent to your data being used in future research studies and substudies.

This trial has three substudies which you may be offered participation in, if you are eligible. The substudies are entirely voluntary and will not affect your participation in the main study.

The PRESTIGE-AF study will also be used to better personalise the predictability of IS and ICH risks for tailoring preventive therapy for future ICH patients. Therefore, we will analyse within a substudy "predictive modelling of risk" information on clinical characteristics from the main PRESTIGE-AF Study (e.g. sociodemographic, stroke severity, comorbidities, concomitant medication, treatment, early and late complication, and outcome). In a second step we will compile this information with data from neuroimaging, blood-based biomarkers and genetics to expand the prediction model, to investigate if the individual risk profile of future patients might be characterized more precisely.

This means that whether you take part in a substudy or not, you can give consent that some of the data that is collected about you for the purposes of the main study will be used within the analysis of the

substudies. This includes the information on medical history, AF diagnosis, details of your ICH and the treatment you have received, drug adherence and the brain imaging scans that you have had as part of your routine care. By agreeing to this you are enabling more research to take place without any further inconvenience to yourself.

Future studies would need to go through the same rigorous ethical screening procedure that we did, to get access to your data. All data shared with future or substudies will be 'pseudonymised'. This means that no information which can identify you will be on the data, just an ID number. The only people who can identify you from that ID number are the direct care team who looks after you.

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 to 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.

SPONSOR

This trial is being sponsored by Imperial College London, they are responsible for the management and conduct of the trial.

ETHICAL REVIEW

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

This research been reviewed and approved by the (Insert details) Research Ethics Committee and the Medicines and Healthcare Products Regulatory Agency (MHRA). The Health Research Authority (HRA) has approved this research to be conducted within the UK National Health Service (NHS).

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:

Kirsten Harvey (Project Manager, Imperial College London)
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Thank you for taking the time to read this information.