PRESTIGE-AF

PREVENTION OF STROKE IN INTRACEREBRAL HAEMORRHAGE SURVIVORS WITH ATRIAL FIBRILLATION

Personal Legal Representative Information Sheet and Consent Form

Chief Investigator: Prof Roland Veltkamp

WE INVITE YOU TO CONSIDER 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.

You are being asked to consider this research study on behalf of a patient, who is your relative or close friend, because they are unable to make the decision for themselves.

- You are free to decide if you wish to make this decision or not.
- You are being asked to consider what the patient would want and should set aside your own personal views when making this decision.
- Before you decide whether to enrol the patient into the study , 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 the patient if this is appropriate and with other relatives or friends.

- You are free to decide whether the patient should take part in this trial. If you choose for the patient not to take part, this will not affect the care they get from their doctors.
- If you do decide for the patient to take part, you can withdraw them from the trial at any time without them being disadvantaged and without giving a reason.
- If in the future, the patient regains capacity to make their own decisions, they will be given all of the information and asked to decide if they want to take part or not. They will be free to withdraw from the trial and can do so without disadvantage.
- 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 for the patient to take part in this study. If you do consent on behalf of the patient to take part, they 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 they go into. One group will receive a direct oral anticoagulant (DOAC) the other group will not receive an anticoagulant. If the patient is in the 'no anticoagulant' group, they can take antiplatelet medication such as aspirin, which is also used for ischaemic stroke prevention, if this is recommended by their 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 the blood. There are four medications which are licenced for use in the EU for prevention in people with AF.

- Apixaban
- Dabigatran
- Edoxaban
- Rivaroxaban

If the patient is randomised to receive a DOAC the doctor will decide which DOAC is right for them. They advise this based on factors such

as the patients age and their kidney function, which can affect which drugs are suitable for them 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 the patients 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.

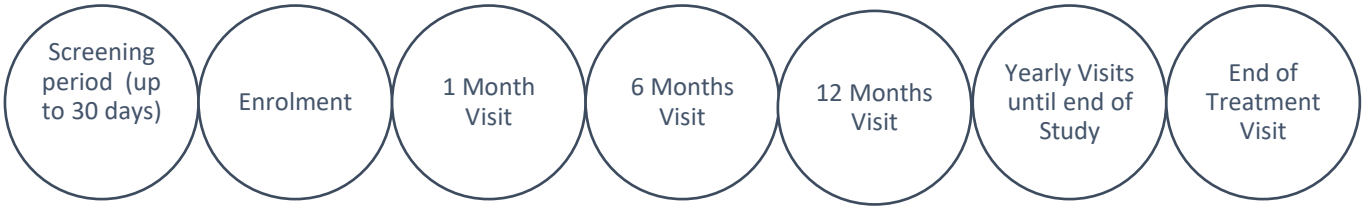
In theory, anticoagulants may increase the risk of having a haemorrhagic stroke but in patients with AF this must be weighed up against the risk of having an ischaemic stroke. Each stroke can have severe consequences but in terms of survival and disability, haemorrhagic strokes are usually more severe 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 the patient taking part in the trial, you will be given time to ask questions and to discuss it with the patient and other family or friends if you wish. If you decide for the patient to take part you will be asked to sign a consent form. After you have signed the form, you can still decide to withdraw the patient 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 the patient is suitable for the trial.

HEALTH TESTS AND MEASUREMENTS

They 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 their general health
- Biochemistry test: to check their liver and kidney function
- Coagulation screen: to check the ability of their blood to clot

If the patient has had these tests done as part of their normal care they 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 the patient's likelihood of having a blood clot and their likelihood of bleeding. These will help us to decide if they are suitable to take part in the study.

We will do an Electrocardiogram (ECG) of their heart, which is a simple test that checks their heart rhythm if they haven't already had one, and we will also measure their weight and height.

Part of these assessments is checking the patient's blood pressure because high blood pressure increases the risk of bleeding into the brain. If they are enrolled into the study their blood pressure will be measured at each study visit. We also recommend that they have their blood pressure regularly checked by their GP. If at any time during the study they have high blood pressure, we will advise them to visit a GP for further advice. If they are found to have uncontrolled high blood pressure during screening, they will not be able to take part in the study until it is under control.

If the patient is a female and they have not reached menopause, we will ask them to give a urine sample for us to take a pregnancy test. If they are enrolled into the trial they will need to take regular pregnancy tests if they are randomised to receive a DOAC. If the patient is pregnant or planning on becoming pregnant during the timeline of the study, they 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 for

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

The doctor will review all of the screening information to ensure that the patient is suitable for the trial. Then we will enter their details into

a computer which will randomise them, and we will tell you and the patient which treatment group they have been allocated to.

FOLLOW UP VISITS

The patient will be seen for follow up visits at the following intervals after their enrolment; 1 month; 6 months; 12 months; 24 months; 36 months and an end of treatment visit. How long they will take part will depend on when they have been enrolled into the trial. They 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 you agree for them to take part.

Follow up visits will usually take place at the hospital but if they are unable to come in it is sometimes possible to do a remote visit or for someone to visit them at home or where they 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 the patient may have while they are on the trial.
- **Medication:** We will ask if the patient has had any changes in the medication that they take.
- **Medication Adherence:** If they are taking a DOAC we will ask about their adherence to taking their medication and we will count their tablets. If they have missed taking any tablets we will discuss this with the patient and any caregivers to try to ensure this doesn't happen.

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

We will reimburse any expenses for travel to study 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 the patient experiences harm or injury as a result of taking part in this study, they will be eligible to claim compensation without

having to prove that Imperial College is at fault. This does not affect their legal rights to seek compensation.

If they are harmed due to someone's negligence, then they may have grounds for a legal action. Regardless of this, if you or they wish to complain, or have any concerns about any aspect of the way the patient has been treated during the course of this study then the investigator should immediately be informed *prestige-af@imperial.ac.uk* The normal National Health Service mechanisms are also available to you and the patient. If you or the patient 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 the patient's information and using it properly. Imperial College London will keep their 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 the patient, their medical records, their GP or other healthcare providers for this research project.

This information will include:

- The patient's name
- Their contact details
- Their NHS Number
- Health information

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

People who do not need to know who the patient is will not be able to see their name or contact details. Their data will have a code number instead.

We will keep all information about the patient safe and secure.

Some of their information will be sent to countries in the European Union. They must follow our rules about keeping the patient's 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 the patient 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 for the patient to take part in a research study, we will use their 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 the patient's 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 the patient's 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 the patient's 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 the patient's 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 the patient's 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

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

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

- If you agree to the patient take part in this study, you will have the option for them to take part in future research using their 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 the patient's 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, or the patient, wish to raise a complaint on how we have handled their 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, or the patient, are not satisfied with our response or believe we are processing their personal data in a way that is not lawful you or the patient, 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 the patient should 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 I am giving this consent based on what I believe would be my relative/friend/partner's wishes. In my opinion they would be willing to participate.	
I understand that participation is voluntary and I or the person I am consenting for are free to withdraw at any time, without giving any reason, without medical care or legal rights being affected.	
I understand that sections of any of my relative/friend/partner's medical notes may be looked at by responsible individuals from NHS or from regulatory authorities where it is relevant to my taking part in this research.	
I give permission for these individuals to access my relative/friend/partner's records that are relevant to this research.	
I agree to my General Practitioner being informed of my relative/friend/partner's participation in the study and consent to any necessary exchange of information about me between their GP and the research team.	
I agree to my relative/friend/partner taking part in the above study.	

I agree that my relative/friend/partner's consent will override my consent when they are able to give informed consent.	☐
I give/do not give *(delete as applicable)* consent for information collected about my relative/friend/partner to be used to support other research in the future, including those outside of the EEA.	☐

Name of Participant

Name of Investigator taking consent	Date	Signature

Name of legal representative	Date	Signature

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