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Platelet receptor glycoprotein VI in thrombus formation and growth in atrial fibrillation and venous thromboembolism

Submission date 11/06/2016	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol
Registration date 02/08/2016	**Overall study status** Completed	[ ] Statistical analysis plan [ ] Results
Last Edited 17/08/2022	**Condition category** Circulatory System	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol

Background and study aims

Platelets are small blood cells that help wounds to heal and help to stop bleeding by forming blood clots. However, if these blood clots form inside blood vessels (thrombosis) they can cause heart attacks, stroke or peripheral vascular disease. Atrial fibrillation (AF) is the term used to refer to common cardiac (or heart) condition which causes an irregular and often abnormally fast heart rate, in some cases faster than 100 beats per minute. The risk of developing the condition increases with age and anyone with the condition is up to 7 times more likely to have a stroke. This is due to the 'fibrillating' movement of the heart chambers causing a build-up of a blood clot in the heart which can then migrate (travel to) to the brain causing a stroke. Similar blood clots can also develop in blood vessels such as veins. People that have blood clots in the veins (for example a deep vein thrombosis) are sad to suffer from venous thromboembolic disease. Venous thromboembolism (VTE) can occur in patients that are hospitalised and are relatively immobile due to the disease that caused their admittance to hospital. It is believed that the way clots formation due to atrial fibrillation and venous thromboembolism is similar, but the involvement of platelets is not fully understood as yet. Cholesterol plaques develop in blood vessels in, for example, older people, people with high blood cholesterol, smokers, people with high blood pressure and people with diabetes. These plaques can rupture, exposing collagen to the blood stream which, in turn, leads to the formation of blood clots. Again, these blood clots can migrate to other places in the body to cause heart attack and stroke. There is currently a mass of evidence which points to glycoprotein VI (GPVI)as the main platelet receptor (a protein involved in platelets adhering, or getting stuck to, collagen) involved in the early stages of blood clot formation due to its interaction with exposed collagen at the sites of plaque rupture. What is not known, however, is its role in blood clot formation in AF and VTE where the platelet clumping and blood clot formation is independent of collagen and plaque rupture. There is recent emerging evidence that fibrin, a compound that which acts to stabilise a blood clot interacts with GPVI and activates platelets. If so this would be a common mechanism for blood clot formation and growth in both AF and venous thromboembolic disease. The GRAFITE (Glycoprotein six Receptor in Atrial FIbrillaiton and ThromboEmbolism) study will investigate the involvement of platelets in blood clot formation. The research team will specifically look at any genetic variances that cause blood clot formation, as well as doing some investigation of the

platelet receptor (glycoprotein VI dimer) and its role in blood clot formation. The research will be carried out in patients admitted to hospital with either atrial fibrillation or venous thromboembolism (for example, deep vein thrombosis), and the role of the Glycoprotein VI receptor plays in the formation of blood clots will be further investigated.

Who can participate?
Adults who have been admitted to hospital with AF or confirmed venous thromboembolic disease.

What does the study involve?
This study involves taking blood samples taken from patients for genetic analysis, platelet activation and glycoprotein VI dimer levels using a method called flow cytometry. This is carried out by laboratory testing on blood samples (from one blood sample per patient). The blood samples are taken on day two of admission, after consent is obtained. Laboratory measurements are then carried out the day the blood is taken, and within 8 hours of collection.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
Cambridge University NHS Foundation Trust and the University of Cambridge (UK)

When is the study starting and how long is it expected to run for?
June 2016 to October 2017

Who is funding the study?
British Heart Foundation

Who is the main contact?
Dr Isuru Induruwa
ii231@cam.ac.uk

Study website
http://www.neurology.cam.ac.uk/

Contact information

Type(s)
Public

Contact name
Dr Isuru Induruwa

Contact details
Clinical Neurosciences
Box 83
Cambridge University Hospitals NHS Foundation Trust
Cambridge
United Kingdom

CB2 0QQ
+44 1223 245151
ii231@cam.ac.uk

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title
Glycoprotein six Receptor in Atrial FIbrillation and ThromboEmbolism

Acronym
GRAFITE

Study objectives
Levels of platelet glycoprotein VI receptor are higher in blood samples of patients with atrial fibrillation and venous thromboembolism compared to healthy normals.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Cambridge East Ethics, 29/11/2016, ref: 16/EE/0436

Study design
Observational cross-sectional cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Not Specified

Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Atrial fibrillation and venous thromboembolism

Interventions
This study involves taking blood samples taken from patients for genetic analysis, platelet activation and glycoprotein VI dimer levels via flow cytometry. This will be carried out by laboratory testing on blood samples (one single blood draw) collected from patients who have atrial fibrillation (either a new diagnosis or known) or venous thromboembolic disease, who are admitted to hospital. The blood samples will be taken on day two of admission, after consent is obtained. Laboratory measurements will be carried out the day of blood draw, within 8h of collection. Measurements will include total glycoprotein VI and dimer levels on platelets, genetic analysis, and blood measurements of known biomarkers of thrombus formation, atrial fibrillation and coagulation.

Intervention Type
Other

Primary outcome measure
Measuring platelet glycoprotein VI dimer levels from blood taken when patients are admitted to hospital with atrial fibrillation or venous thromboembolism, as measured by mean fluorescence on flow cytometry

Secondary outcome measures
1. Measure the correlation between glycoprotein VI dimer mean florescence intensity on flow cytometry with levels of known common blood biomarkers for atrial fibrillation, coagulation and stroke (d-dimer, hs-CRP, BNP)
2. Measure the correlation between glycoprotein VI dimer levels as measured by mean fluorescence on flow cytometry and estimated risk of stroke as stratified by the CHADS2-VASC2 score calculated at the time of participant involvement
3. Determine the genetic basis for atrial fibrillation and venous thromboembolism and a therefore look for a genetic basis for possible pre-disposition to stroke

Overall study start date
15/06/2016

Completion date
30/09/2019

Eligibility

Key inclusion criteria
1. Patients with a new diagnosis of AF and those with persistent or paroxysmal AF, whether they are on anticoagulation or not
2. Patients with confirmed venous thromboembolic disease
3. Admitted under a medical team to Cambridge University Hospitals

Participant type(s)

Patient

Age group
Adult

Sex
Both

Target number of participants
150

Total final enrolment
79

Key exclusion criteria
1. No clear confirmation of the presence of atrial fibrillation in medical notes or ECG (for AF patients)
2. No confirmed venous thromboembolic disease on any imaging modality (only for those with suspected VTE)
3. Age less than 18 years
4. Pregnancy
5. Active and known malignancy
6. Known platelet disorder
7. Known HIV/AIDS
8. Known hepatitis B or hepatitis C infection
9. Admitted with a transient ischaemic attack or stroke – ischaemic or haemorrhagic
10.Patients who lack capacity

Date of first enrolment
01/10/2016

Date of final enrolment
01/10/2017

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Cambridge University NHS Foundation Trust
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Department of Biochemistry, University of Cambridge
Downing Site
Cambridge
United Kingdom
CB2 1QJ

Sponsor information

Organisation
British Heart Foundation

Sponsor details
Division of Cardiovascular Medicine
ACCI, Level 6, Box 110
Addenbrooke's Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Sponsor type
Charity

ROR
https://ror.org/02wdwnk04

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date
01/02/2023

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 2	10/11/2016	15/08/2022	No	No
HRA research summary			28/06/2023	No	No