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Treatment with medications that prevent the formation of blood clots, in the primary prevention of heart disease in patients with a stable lung condition called Chronic Obstructive Pulmonary Disease (COPD)

Submission date 21/10/2015	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 21/10/2015	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 08/11/2023	**Condition category** Respiratory	[_] Individual participant data

Plain English summary of protocol

Background and study aims
Chronic obstructive pulmonary disease (COPD) is the collective name for a group of diseases which affect the lungs. People who suffer from COPD have difficulty breathing, which gets worse over time. This is because the airways become narrowed or blocked, and the air sacs (alveoli) in the lungs are destroyed or lose their ability to stretch. The main cause of COPD is smoking, which over time permanently damages the lining of the lungs. Many studies have shown that people with COPD have a greater risk of developing heart and blood vessel disease (cardiovascular disease) which can lead to a heart attack. When a person is suffering from cardiovascular disease (CVD), fatty substances (plaque) build up inside blood vessels causing them to become narrowed. Platelets (a component of blood) “stick” to the walls of these narrowed blood vessels, causing blockages (occlusion) that can lead to a heart attack. Ticagrelor is a medication which works by slowing and stopping platelets from sticking to the blood vessel walls. It is usually taken with aspirin, which makes this more effective by “thinning” the blood. These medications are often used in CVD patients and have been shown to be very effective. Currently there is very little information about the best way to treat COPD patients who are at risk of heart disease. The aim of this study is to find out whether treatment with ticagrelor and /or aspirin can help to lower the risk of heart disease in COPD patients.

Who can participate?
Adults who have smoked for at least 10 years with signs of COPD.

What does the study involve?
Participants are randomly allocated to one of three treatment groups or a control group. Those in the treatment groups are given aspirin and/or ticagrelor to take, and those in the control group are given a placebo (dummy pill). At the initial visit, participants will undergo a blood test, a lung function test, an ultrasound scan, they will have their stiffness of the blood vessels

measured and they will be asked to complete questionnaires. Participants who are receiving the treatment attend follow up visits at 1, 3 and 6 months to see whether the medication is having any effect. The blood tests and questionnaires are repeated at a 6 month follow up visit for both groups.

What are the possible benefits and risks of participating?
There are no direct benefits to the patient for participating in this study. However, their participation in this study may add to the medical knowledge about how to treat COPD patients who are at risk of future heart problems. There are minor risks related to taking the study medications (asprin and ticagrelor), however the benefits have been judged to outweigh the risks.

Where is the study run from?
Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
September 2015 to November 2017

Who is funding the study?
AstraZeneca UK Limited (UK)

Who is the main contact?
Catherine Brennand
cath.brennand@ncl.ac.uk

Contact information

Type(s)
Public

Contact name
Ms Catherine Brennand

Contact details
Newcastle Clinical Trials Unit
Faculty of Medical Sciences
1-4 Claremont Terrace
Newcastle University
Newcastle Upon Tyne
United Kingdom
NE2 4AE
+44 (0)191 208 7258
cath.brennand@ncl.ac.uk

Additional identifiers

EudraCT/CTIS number
2014-005475-86

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 19244

Study information

Scientific Title
Anti-platelet therapy in the primary prevention of cardiovascular disease in patients with chronic obstructive pulmonary disease

Acronym
APPLE-COPD:ICON 2

Study objectives
The aim of this study is to find out whether ticagrelor and/or aspirin are effective treatments in the primary prevention of cardiovascular disease in patients with chronic obstructive pulmonary disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
First Medical Research Ethics Commitee, 26/05/2015, ref: 15/NE/0155

Study design
Randomized; Interventional; Design type: Treatment

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Topic: Cardiovascular disease, Respiratory disorders; Subtopic: Cardiovascular (all Subtopics), Respiratory (all Subtopics); Disease: Cardiovascular, Respiratory

Interventions

Patients who meet the inclusion criteria with a QRISK2 score >20% will be randomised to the treatment arm. A stratified blocked treatment allocation system is used to randomise patients into four groups who each receive a different treatment for six months:

1. Aspirin (75 mg once daily dose) and Ticagrelor (90 mg twice daily dose)
2. Aspirin (75 mg once daily dose) and placebo
3. Ticagrelor (90 mg twice daily dose) and placebo
4. Placebo alone

Block size will not be disclosed to the investigators. Randomisation will be administered centrally via the Newcastle Clinical Trials Unit using a secure web-based system.
Patients will attend follow-up visits at the Clinical Research Facility, Royal Victoria Infirmary at 1-month, 3-months and 6-months and then followed up clinically for up to 1 year.

Patients with a QRISK2 score <20% will be allocated to the observational cohort of the study, they will undergo the baseline procedures, including blood tests and will be followed up again at 1 year. Patients in the observational cohort will not undergo follow-up visits at 1 month, 3 months and 6 months.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Aspirin, ticagrelor

Primary outcome measure
Inhibition of adenosine disphosphate-induced platelet aggregation measured using the multiplate test at baseline and 6 months.

Secondary outcome measures
1. Changes in inflammatory markers including fibrinogen, hsCRP, TNF alpha, IL-6, MPO is measured from blood samples taken at baseline and 6 months
2. Changes in carotid intima media thickness measured using an ultrasound probe and vascular stiffness measured using a specialised pressure cuff similar to a blood pressure cuff at baseline and 6 months
3. Quality of life measured using questionnaires (EQ5D-5L, St. George's COPD questionnaire) at baseline and 6 months

Overall study start date
04/09/2015

Completion date
10/11/2017

Eligibility

Key inclusion criteria

1. Aged 18 years or over
2. Abnormal spirometry with FEV1<80% and FEV1/FVC ratio <70% of predicted
3. Smoking history that is 10 years or greater (current or ex smokers can be included)
4. Patient has the capacity to consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 240; UK Sample Size: 240; Description: Interventional arm - 120 Observational arm - 120

Total final enrolment
120

Key exclusion criteria
1. Any condition that is being concurrently treated through anticoagulation or antiplatelet therapy (atrial fibrillation, deep vein thrombosis, valve prosthesis, recent myocardial infarction, use of drug eluting stents)
2. Other specific contraindications to management with antiplatelet medication (bleeding risks, allergies)
3. Any contraindication for Aspirin and Ticagrelor use
4. Other concurrent terminal illnesses with life expectancy less than 1 year (congestive cardiac failure, carcinoma etc.)
5. Current involvement in another clinical trial or exposure to another IMP within the previous 30 days
6. COPD with an atypical cause (e.g. A1antitrypsin deficiency)
7. Planned/ Expected major surgery where anti-platelet therapy would be ceased
8. Pregnancy, planned pregnancy or current breastfeeding
9. Patient is unable to provide informed consent
10. Younger than 18 years

Date of first enrolment
04/09/2015

Date of final enrolment
31/05/2017

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Royal Victoria Infirmary
Newcastle upon Tyne Hospitals NHS Foundation Trust
Queen Victoria Road
Newcastle Upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Freeman Hospital
Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Road
Newcastle Upon Tyne
United Kingdom
NE7 7DN

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

Sponsor details
Freeman Hospital
Freeman Road
Newcastle upon Tyne
England
United Kingdom
NE7 7DN

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in peer reviewed journals as well as presentation of data at national and international meetings. Results of the study will also be reported to the sponsor and funder. Participants will be informed about their treatment and their contribution to the study at the end of the study, including a lay summary of the results.

Intention to publish date
31/12/2019

Individual participant data (IPD) sharing plan
There currently are no provisions or a plan in place for data sharing for APPLE-COPD. The data are held by NCTU on behalf of the Sponsor. NCTU are currently developing a data sharing policy and it may be possible to make data available in the future.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	26/05/2018	17/05/2019	Yes	No
Basic results			17/06/2020	No	No
HRA research summary			28/06/2023	No	No
Results article		05/08/2019	08/11/2023	Yes	No