Clinical trial results:
Is cessation of clopidogrel therapy associated with rebound of platelet activity in stable vascular disease patients?

Summary

EudraCT number	2007-007638-21
Trial protocol	GB
Global end of trial date	24 July 2012

Results information

Result version number	v1 (current)
This version publication date	19 August 2018
First version publication date	19 August 2018

Trial information

Trial identification

Sponsor protocol code	CR2

Additional study identifiers

ISRCTN number	ISRCTN77887299
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NHS Grampian
Sponsor organisation address	R&D Office, Foresterhill House Annexe, Aberdeen, United Kingdom, AB25 2ZB
Public contact	Gail Holland, NHS Grampian, 01224 555076, researchgovernance@abdn.ac.uk
Scientific contact	Gail Holland, NHS Grampian, 01224 555076, researchgovernance@abdn.ac.uk
Sponsor organisation name	University of Aberdeen
Sponsor organisation address	R&D Office, Foresterhill House Annexe, Aberdeen, United Kingdom, AB25 2ZB
Public contact	Professor Julie Brittenden, University of Aberdeen, 01224 551123, researchgovernance@abdn.ac.uk
Scientific contact	Professor Julie Brittenden, University of Aberdeen, 01224 551123, researchgovernance@abdn.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 January 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 July 2012
Global end of trial reached?	Yes
Global end of trial date	24 July 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary aim of this study is to identify whether there is evidence for a "rebound" effect on platelet markers associated with cessation of clopidogrel therapy. We propose to address this in patients with stable cardiovascular disease by means of a mechanistic study.

Protection of trial subjects:

Ethical approval was obtained (NOSRES 08/S0801/087), and each patient gave written informed consent.

Background therapy:

The thienopyridine derivative, clopidogrel is an effective inhibitor of platelet activation and aggregation as a result of its selective and irreversible blockade of the P2Y12 receptor1. Combination antiplatelet therapy with clopidogrel and aspirin has been shown to be an effective strategy in patients with acute coronary syndromes and in those undergoing percutaneous interventions.

Evidence for comparator:

A placebo group is included to determine whether any detected change in platelet activation is due to the clopidogrel therapy rather than changes that may occur over the course of the study in this population of patients.

Actual start date of recruitment	08 October 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 172
Worldwide total number of subjects	172
EEA total number of subjects	172

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	75
From 65 to 84 years	97
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients who meet the criteria of the study will be identified from clinical databases of patients with stable vascular disease who have formerly attended the Cardiology and Vascular Surgery Unit at Aberdeen Royal Infirmary (ARI).

Pre-assignment

Screening details:

Participants will be invited by letter with information sheet enclosed. Prepaid envelope will be included to facilitate a reply. Those who reply positively will be offered an appointment by telephone by the research nurse and an opportunity to ask questions about the study.

Period 1

Period 1 title	Clopidogrel vs Placebo (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Clopidogrel

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Clopidogrel
Investigational medicinal product code	
Other name	Plavix
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

75 mg daily for 30 days (containing Clopidogrel tablets 75mg diluted with Lactose PhEur enclosed in a hard capsule shell).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75mg daily for 30 days (containing Lactose PhEur 540mg to match the active)

Arm title	Placebo

Arm description: -

Arm type	Placebo

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Clopidogrel	Placebo
Started	88	84
Completed	88	84

Baseline characteristics

Reporting groups	
Reporting group title	Clopidogrel vs Placebo

Reporting group description: -

Reporting group values	Clopidogrel vs Placebo	Total	
Number of subjects	172	172	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	75	75	
From 65-84 years	97	97	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	84	84	
Male	88	88	

End points

End points reporting groups

Reporting group title	Clopidogrel
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: ADP -stimulated platelet fibrinogen binding

End point title	ADP -stimulated platelet fibrinogen binding
End point description:	
End point type	Primary
End point timeframe:	

Blood samples were taken at pre-treatment baseline, on treatment just before discontinuation of study drug, and on days 7, 14, and 28 after discontinuation.

End point values	Clopidogrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	84		
Units: 10 umol/l				
number (not applicable)	88	84		

Statistical analyses

Statistical analysis title	Final Results

Statistical analysis description:

Descriptive results were produced for all outcomes, but statistical testing was only performed for the primary and secondary outcomes. The primary research question was addressed using a mixed model procedure, xt-mixed in Stata (21), using 7 models, 1 for each primary and secondary outcome measure, excluding the on-treatment timepoint but including baseline and 7, 14, and 28 days after treatment.

Comparison groups	Clopidogrel v Placebo
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Within 24hrs.

Assessment type	Systematic

Dictionary used

Dictionary name	None
Dictionary version	0

Reporting groups

Reporting group title	Total AE

Reporting group description: -

Serious adverse events	Total AE		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 81 (3.70%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Chest pain			
subjects affected / exposed[1]	1 / 1 (100.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chest tightness			
subjects affected / exposed[2]	1 / 1 (100.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Vasovagal			
subjects affected / exposed[3]	1 / 1 (100.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
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Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Total AE		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 81 (58.02%)		
Cardiac disorders			
Tightness in gullet/chest			
subjects affected / exposed[4]	1 / 1 (100.00%)		
occurrences (all)	1		
Atrial fibrillation			
subjects affected / exposed[5]	1 / 1 (100.00%)		
occurrences (all)	1		
Angina unstable			
subjects affected / exposed[6]	1 / 1 (100.00%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed[7]	1 / 1 (100.00%)		
occurrences (all)	1		
Myocardial infarction	Additional description: Mild		
subjects affected / exposed[8]	1 / 1 (100.00%)		
occurrences (all)	1		
Irregular heart beat			
subjects affected / exposed[9]	1 / 1 (100.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Tooth infection			
subjects affected / exposed[10]	1 / 1 (100.00%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed[11]	1 / 1 (100.00%)		
occurrences (all)	1		
Shoulder pain			
subjects affected / exposed[12]	3 / 3 (100.00%)		
occurrences (all)	3		
Bruising			

subjects affected / exposed[13]	6 / 6 (100.00%)		
occurrences (all)	6		
Thigh pain			
subjects affected / exposed[14]	1 / 1 (100.00%)		
occurrences (all)	1		
Increased sweats			
subjects affected / exposed[15]	1 / 1 (100.00%)		
occurrences (all)	1		
swelling of polypoidas			
subjects affected / exposed[16]	1 / 1 (100.00%)		
occurrences (all)	1		
Tiredness			
subjects affected / exposed[17]	1 / 1 (100.00%)		
occurrences (all)	1		
Knee pain			
subjects affected / exposed[18]	1 / 1 (100.00%)		
occurrences (all)	1		
Sore foot			
subjects affected / exposed[19]	1 / 1 (100.00%)		
occurrences (all)	1		
Arm pain			
subjects affected / exposed[20]	1 / 1 (100.00%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed[21]	1 / 1 (100.00%)		
occurrences (all)	1		
redness in ear			
subjects affected / exposed[22]	1 / 1 (100.00%)		
occurrences (all)	1		
Bad Tempered			
subjects affected / exposed[23]	1 / 1 (100.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Increased hot flushes			
subjects affected / exposed[24]	1 / 1 (100.00%)		
occurrences (all)	1		

Epistaxis			
subjects affected / exposed[25]	5 / 5 (100.00%)		
occurrences (all)	5		
Increased bleeding			
subjects affected / exposed[26]	1 / 1 (100.00%)		
occurrences (all)	1		
Vasovagul			
subjects affected / exposed[27]	1 / 3 (33.33%)		
occurrences (all)	3		
Immune system disorders			
Common Cold			
subjects affected / exposed[28]	8 / 8 (100.00%)		
occurrences (all)	8		
Cold sore			
subjects affected / exposed[29]	1 / 1 (100.00%)		
occurrences (all)	1		
Viral illness			
subjects affected / exposed[30]	1 / 1 (100.00%)		
occurrences (all)	1		
sore throat			
subjects affected / exposed[31]	1 / 1 (100.00%)		
occurrences (all)	1		
Eye disorders			
Blood shot eye			
subjects affected / exposed[32]	1 / 1 (100.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed[33]	3 / 3 (100.00%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed[34]	4 / 4 (100.00%)		
occurrences (all)	4		
Phlebitis			
subjects affected / exposed[35]	1 / 1 (100.00%)		
occurrences (all)	1		
Stomach upset			

subjects affected / exposed[36] occurrences (all)	1 / 1 (100.00%) 1		
Diverticulitis subjects affected / exposed[37] occurrences (all)	1 / 1 (100.00%) 1		
acid reflux subjects affected / exposed[38] occurrences (all)	1 / 1 (100.00%) 1		
Diarrhoea and vomiting subjects affected / exposed[39] occurrences (all)	1 / 1 (100.00%) 1		
Vomiting subjects affected / exposed[40] occurrences (all)	1 / 1 (100.00%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed[41] occurrences (all)	2 / 2 (100.00%) 2		
Worsening of COPD subjects affected / exposed[42] occurrences (all)	1 / 1 (100.00%) 1		
Skin and subcutaneous tissue disorders Itchy skin subjects affected / exposed[43] occurrences (all)	2 / 2 (100.00%) 2		
Renal and urinary disorders Urinary tract infection subjects affected / exposed[44] occurrences (all)	1 / 1 (100.00%) 1		
Endocrine disorders Diabetes mellitus subjects affected / exposed[45] occurrences (all)	1 / 1 (100.00%) 1		
Musculoskeletal and connective tissue disorders Increased arthritis pain			

subjects affected / exposed[46]	1 / 1 (100.00%)		
occurrences (all)	1		
Infections and infestations			
Anus infection			
subjects affected / exposed[47]	1 / 1 (100.00%)		
occurrences (all)	1		
Chest infection			
subjects affected / exposed[48]	4 / 4 (100.00%)		
occurrences (all)	4		
Infection			
subjects affected / exposed[49]	2 / 2 (100.00%)		
occurrences (all)	2		
Infected bursitis			
subjects affected / exposed[50]	1 / 1 (100.00%)		
occurrences (all)	1		

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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The main limitation of the present study was that patients received clopidogrel for only 1 month, so chronic changes may have been missed.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24211510