Clinical trial results:
Pharmacokinetics and Pharmacodynamics of Platelet P2Y12 Inhibitors in Patients Undergoing Percutaneous Coronary Intervention (PCI) for Acute Myocardial Infarction: A Pilot Study

Summary

EudraCT number	2014-004238-25
Trial protocol	GB
Global end of trial date	30 November 2015

Results information

Result version number	v1 (current)
This version publication date	11 July 2019
First version publication date	11 July 2019

Trial information

Trial identification

Sponsor protocol code	2012-004-0402-CARD

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02376283
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Royal Wolverhampton NHS Trust
Sponsor organisation address	New Cross Hospital, Wolverhampton, United Kingdom, WV10 0QP
Public contact	James Cotton, The Royal Wolverhampton NHS Trust, 01902 307999, jamescotton@nhs.net
Scientific contact	James Cotton, The Royal Wolverhampton NHS Trust, 01902 307999, jamescotton@nhs.net

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	31 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2015
Global end of trial reached?	Yes
Global end of trial date	30 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To demonstrate the degree of platelet inhibition by clopidogrel, prasugrel and ticagrelor given acutely before emergency primary angioplasty for ST-elevation myocardial infarction (STEMI), during the procedure and in the following 4 hours, to determine whether the condition of STEMI per se reduces the efficacy of orally administered P2Y12 inhibitors.

2) To determine the degree and time-course of platelet inhibition of an oral P2Y12 inhibitor (clopidogrel/prasugrel/ticagrelor) given acutely before emergency primary angioplasty for STEMI, during the procedure and in the following 4 hours. This will be compared with a cohort of patients presenting with non-ST elevation myocardial infarction (NSTEMI) treated with either oral P2Y12 inhibitor to determine whether the condition of STEMI per se reduces the efficacy of ticagrelor treatment.

Protection of trial subjects:

All drugs were prescribed and administered in line with their licensed indications, and in accordance with local and national guideline recommendations. All patients were monitored for adverse events as per routine clinical practice. Patients were not considered for inclusion if they were unable to provide written or verbal informed consent, were under 18 years of age, had a documented allergy to aspirin or clopidogrel/prasugrel/ticagrelor.

Background therapy:

All patients were administered oral aspirin 300mg as a single dose following by a maintenance dose of 75mg daily. The oral P2Y12 inhibitor dose was in line with licensed/guideline recommendations; clopidogrel 600mg loading followed by 75mg daily maintenance, prasugrel 60mg loading followed by 10mg daily and ticagrelor 180mg loading followed by 90mg twice daily thereafter. Background antithrombotic therapy with unfractionated heparin was administered during the procedure.

Evidence for comparator:

The comparative efficacy of orally administered P2Y12 inhibitors was determined using the point of care VerifyNow assay and expressed as a measure of P2Y12 reaction unit (PRU). The PRU measurement provides an indication of the degree of platelet inhibition achieved following the administration of a P2Y12 inhibitor loading dose on admission.

Actual start date of recruitment	10 June 2013
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: 87
Worldwide total number of subjects	87
EEA total number of subjects	87

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)	38
From 65 to 84 years	42
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Location: Cardiology catheter laboratory and cardiology ward, Heart and Lung Centre, The Royal Wolverhampton Hospital NHS Trust, Wolverhampton, UK

Recruitment period: 2 years and 10 months (34 months)

Pre-assignment

Screening details:

Clopidogrel and prasugrel were included only as the P2Y12 inhibitors under investigation initially. Amendment incorporated ticagrelor as addition. Recruitment to the prasugrel NSTEMI arm was unusually slow; therefore indications for use were changed to reflect the manufacturers recommendations and not NICE guidance.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Clopidogrel

Arm description:

All STEMI and NSTEMI patients were administered a clopidogrel 600mg loading dose following confirmation of their diagnosis and receipt of verbal assent/informed consent prior to whole blood samples being collected for pharmacodynamic and pharmacokinetic assessment of the degree and time course of platelet inhibition.

Arm type	pharmacological drug handling
Investigational medicinal product name	Clopidogrel hydrogen sulphate
Investigational medicinal product code	B01AC-04
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

600mg one off, loading dose, followed by 75mg daily maintenance dose for 12 months

Arm title	Prasugrel

Arm description:

All STEMI and NSTEMI patients were administered a prasugrel 60mg loading dose following confirmation of their diagnosis and receipt of verbal assent/informed consent prior to whole blood samples being collected for pharmacodynamic and pharmacokinetic assessment of the degree and time course of platelet inhibition.

Arm type	drug handling of prasugrel
Investigational medicinal product name	Prasugrel hydrochloride
Investigational medicinal product code	B01AC22
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Prasugrel 60mg one-off loading dose following by a 10mg daily maintenance dose for 12 months
(For the purposes of our protocol, prasugrel was prescribed and administered only in those patients over 60kg and under the age of 75 years, as per the manufacturers recommendations)

Arm title	Ticagrelor

Arm description:

All STEMI and NSTEMI patients were administered a prasugrel 60mg loading dose following confirmation of their diagnosis and receipt of verbal assent/informed consent prior to whole blood samples being collected for pharmacodynamic and pharmacokinetic assessment of the degree and time course of platelet inhibition.

Arm type	pharmacological drug handling of ticagrelor
Investigational medicinal product name	Ticagrelor
Investigational medicinal product code	B01AC24
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ticagrelor 180mg one-off loading dose, followed by 90mg twice daily maintenance dose for 12 months.

Number of subjects in period 1	Clopidogrel	Prasugrel	Ticagrelor
Started	27	30	30
Completed	27	30	30

Baseline characteristics

Reporting groups	
Reporting group title	Clopidogrel
Reporting group description:	
All STEMI and NSTEMI patients were administered a clopidogrel 600mg loading dose following confirmation of their diagnosis and receipt of verbal assent/informed consent prior to whole blood samples being collected for pharmacodynamic and pharmacokinetic assessment of the degree and time course of platelet inhibition.	
Reporting group title	Prasugrel
Reporting group description:	
All STEMI and NSTEMI patients were administered a prasugrel 60mg loading dose following confirmation of their diagnosis and receipt of verbal assent/informed consent prior to whole blood samples being collected for pharmacodynamic and pharmacokinetic assessment of the degree and time course of platelet inhibition.	
Reporting group title	Ticagrelor
Reporting group description:	
All STEMI and NSTEMI patients were administered a prasugrel 60mg loading dose following confirmation of their diagnosis and receipt of verbal assent/informed consent prior to whole blood samples being collected for pharmacodynamic and pharmacokinetic assessment of the degree and time course of platelet inhibition.	

Reporting group values	Clopidogrel	Prasugrel	Ticagrelor
Number of subjects	27	30	30
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	19	13
From 65-84 years	15	11	16
85 years and over	3	0	1
Gender categorical Units: Subjects			
Female	8	5	6
Male	19	25	24
Pharmacodynamic assessment of degree of platelet inhibition			
Pharmacodynamic assessment of degree of platelet inhibition as determined by VerifyNow point of care assay and expressed as P2Y12 reaction units (PRU)			
Units: Subjects			
STEMI	13	15	15
NSTEMI	14	15	15

Reporting group values	Total		
Number of subjects	87		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	41		
From 65-84 years	42		
85 years and over	4		
Gender categorical Units: Subjects			
Female	19		
Male	68		
Pharmacodynamic assessment of degree of platelet inhibition			
Pharmacodynamic assessment of degree of platelet inhibition as determined by VerifyNow point of care assay and expressed as P2Y12 reaction units (PRU)			
Units: Subjects			
STEMI	43		
NSTEMI	44		

End points

End points reporting groups

Reporting group title	Clopidogrel

Reporting group description:

All STEMI and NSTEMI patients were administered a clopidogrel 600mg loading dose following confirmation of their diagnosis and receipt of verbal assent/informed consent prior to whole blood samples being collected for pharmacodynamic and pharmacokinetic assessment of the degree and time course of platelet inhibition.

Reporting group title	Prasugrel

Reporting group description:

All STEMI and NSTEMI patients were administered a prasugrel 60mg loading dose following confirmation of their diagnosis and receipt of verbal assent/informed consent prior to whole blood samples being collected for pharmacodynamic and pharmacokinetic assessment of the degree and time course of platelet inhibition.

Reporting group title	Ticagrelor

Reporting group description:

All STEMI and NSTEMI patients were administered a prasugrel 60mg loading dose following confirmation of their diagnosis and receipt of verbal assent/informed consent prior to whole blood samples being collected for pharmacodynamic and pharmacokinetic assessment of the degree and time course of platelet inhibition.

Subject analysis set title	Ticagrelor parent compound
Subject analysis set type	Per protocol

Subject analysis set description:

STEMI/NSTEMI patients.
Ticagrelor was used in our centre only after the use of prasugrel was discontinued. Other analysis with active metabolite.

Primary: Pharmacodynamic assessment of degree of platelet inhibition as determined by VerifyNow point of care assay and expressed as P2Y12 reaction units (PRU)

End point title	Pharmacodynamic assessment of degree of platelet inhibition as determined by VerifyNow point of care assay and expressed as P2Y12 reaction units (PRU)

End point description:

Pharmacodynamic assessment of degree of platelet inhibition as determined by VerifyNow point of care assay and expressed as P2Y12 reaction units (PRU)

End point type	Primary

End point timeframe:

240 minutes

End point values	Clopidogrel	Prasugrel	Ticagrelor	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	30	30	
Units: PRU				
arithmetic mean (standard deviation)				
STEMI at 20 mins	270.23 (± 38.56)	247.73 (± 48.78)	256.73 (± 50.81)	
STEMI at balloon inflation	286.46 (± 33.12)	253.73 (± 57.17)	257.93 (± 61.12)	
STEMI at 60 mins	293.46 (± 31.68)	262.87 (± 43.43)	225.20 (± 82.70)	

STEMI at 240 mins	226.42 (± 69.44)	128.64 (± 89.16)	176.27 (± 84.92)	
NSTEMI at 20 mins	213.21 (± 51.74)	125.80 (± 89.34)	172.80 (± 92.54)	
NSTEMI at 60 mins	227.36 (± 61.19)	76.93 (± 99.24)	114.20 (± 122.22)	
NSTEMI at 240 mins	214.00 (± 69.98)	31.87 (± 45.52)	23.00 (± 18.94)	

Statistical analyses

Statistical analysis title	Pharmacodynamic assessment - VerifyNow

Statistical analysis description:

Continuous variables were expressed as mean ± SD and categorical variables as frequencies (%). Continuous variables were analysed individually using student's independent sample t-tests. Categorical variables were assessed using separate Fisher's exact (Chi-sqaure) test.

Comparison groups	Clopidogrel v Prasugrel v Ticagrelor
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	< 0.05 [2]
Method	t-test, 2-sided
Variability estimate	Standard deviation

Notes:

[1] - A p value < 0.05 was considered to be statistically significant.
Comparison of means between groups was assessed using analysis of variance (ANOVA) technique. ANOVA allowed for a comparison of more than two means and enabled an assessment to be made of the relationship between, different drugs (clopidogrel vs prasugrel vs ticagrelor), different clinical states (STEMI vs NSTEMI/UA) and different time points.
[2] - Considered significant

Primary: Pharmacokinetic quantification of the plasma concentration of clopidogrel and prasugrel active metabolite and ticagrelor parent compound and active metabolite

End point title	Pharmacokinetic quantification of the plasma concentration of clopidogrel and prasugrel active metabolite and ticagrelor parent compound and active metabolite

End point description:

Pharmacokinetic quantification of the plasma concentration of clopidogrel and prasugrel active metabolite and ticagrelor parent compound and active metabolite assessed using liquid chromatography in tandem with mass spectrometry (LC-MS/MS) and expressed as ng/ml

End point type	Primary

End point timeframe:

240 minutes

End point values	Clopidogrel	Prasugrel	Ticagrelor	Ticagrelor parent compound
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	27	30	30	30
Units: ng/ml				
arithmetic mean (standard deviation)				
STEMI at 20 mins	39.12 (± 16.17)	14.27 (± 8.80)	0.16 (± 0.16)	9.04 (± 4.12)
STEMI at balloon inflation	107.83 (± 44.08)	24.20 (± 13.07)	1.64 (± 1.17)	28.56 (± 12.58)
STEMI at 60 mins	71.02 (± 27.21)	36.86 (± 13.27)	14.43 (± 7.28)	47.13 (± 24.09)
STEMI at 240 mins	32.41 (± 6.71)	38.44 (± 7.59)	53.38 (± 25.21)	84.92 (± 42.00)
NSTEMI at 20 mins	41.99 (± 25.27)	515.80 (± 126.84)	7.72 (± 5.10)	22.78 (± 10.27)
NSTEMI at 60 mins	93.35 (± 49.65)	194.59 (± 29.97)	58.40 (± 25.41)	84.13 (± 34.02)
NSTEMI at 240 mins	27.71 (± 6.90)	36.80 (± 4.59)	113.59 (± 19.20)	140.61 (± 36.31)

Statistical analyses

Statistical analysis title	Pharmacokinetic quantification

Statistical analysis description:

Pharmacokinetic quantification of the plasma concentration of clopidogrel and prasugrel active metabolite and ticagrelor parent compound and active metabolite assessed using liquid chromatography in tandem with mass spectrometry (LC-MS/MS) and expressed as ng/ml.
Continuous variables expressed as mean ± SEM and categorical variables as frequencies (%).
Continuous variables were analysed individually using student's independent sample t-tests.

Comparison groups	Clopidogrel v Prasugrel v Ticagrelor v Ticagrelor parent compound
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	< 0.05 [4]
Method	t-test, 2-sided
Variability estimate	Standard error of the mean

Notes:

[3] - Categorical variables assessed using separate Fisher's exact (Chi-sqaure) test. A p value < 0.05 considered to be statistically significant. Comparison of means between groups assessed using ANOVA technique. ANOVA allowed comparison of more than two means and enabled assessment of the relationship between different drugs (clopidogrel active metabolite vs prasugrel active metabolite vs ticagrelor parent compound & active metabolite), different clinical states and different time points.
[4] - Considered significant

Secondary: Pharmacodynamic assessment of degree of platelet inhibition as determined by VASP flow cytometry and expressed as %PRI (platelet reactivity index)

End point title	Pharmacodynamic assessment of degree of platelet inhibition as determined by VASP flow cytometry and expressed as %PRI (platelet reactivity index)

End point description:

Pharmacodynamic assessment of degree of platelet inhibition as determined by VASP flow cytometry and expressed as %PRI (platelet reactivity index)

End point type	Secondary

End point timeframe:

240 minutes

End point values	Clopidogrel	Prasugrel	Ticagrelor	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	30	30	
Units: %PRI				
arithmetic mean (standard deviation)				
STEMI at 20 mins	76.29 (± 8.77)	46.25 (± 13.91)	79.75 (± 9.20)	
STEMI at balloon inflation	74.86 (± 9.00)	41.13 (± 12.71)	74.63 (± 11.42)	
STEMI at 60 mins	71.57 (± 11.68)	50.50 (± 11.88)	76.25 (± 11.12)	
STEMI at 240 mins	63.14 (± 13.26)	57.00 (± 10.39)	51.38 (± 14.06)	
NSTEMI at 20 mins	75.17 (± 2.74)	33.27 (± 10.66)	62.00 (± 8.79)	
NSTEMI at 60 mins	76.75 (± 4.35)	21.91 (± 9.72)	33.17 (± 17.73)	
NSTEMI at 240 mins	61.83 (± 5.82)	15.18 (± 5.85)	20.17 (± 10.48)	

Statistical analyses

Statistical analysis title	Pharmacodynamic assessment - VASP

Statistical analysis description:

Continuous variables were expressed as mean ± SD and categorical variables as frequencies (%). Continuous variables were analysed individually using student’s independent sample t-tests. Categorical variables were assessed using separate Fisher’s exact (Chi-sqaure) test.

Comparison groups	Clopidogrel v Prasugrel v Ticagrelor
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	< 0.05 [6]
Method	t-test, 2-sided
Variability estimate	Standard deviation

Notes:

[5] - A p value < 0.05 was considered to be statistically significant.
Comparison of means between groups was assessed using analysis of variance (ANOVA) technique. ANOVA allowed for a comparison of more than two means and enabled an assessment to be made of the relationship between, different drugs (clopidogrel vs prasugrel vs ticagrelor), different clinical states (STEMI vs NSTEMI/UA) and different time points.

[6] - Considered significant

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

24 hours

Adverse event reporting additional description:

An SAE form will be completed and submitted to R&D by the chief investigator within 24 hours of an event being noted.

Assessment type	Systematic

Dictionary used

Dictionary name	SNOMED CT
Dictionary version	UK

Reporting groups

Reporting group title	Clopidogrel

Reporting group description:

STEMI/NSTEMI treatment in patients who are not eligible for treatment with prasugrel/ticagrelor (based on clinical characteristics and as per study protocol)

Reporting group title	Prasugrel

Reporting group description:

STEMI/NSTEMI patients over the 60kg in weight and under 75 years of age.
(Prasugrel use was discontinued in our centre following a change in protocol to ticagrelor)

Reporting group title	Ticagrelor

Reporting group description:

STEMI/NSTEMI patients.
(Ticagrelor was used in our centre only after the use of prasugrel was discontinued)

Serious adverse events	Clopidogrel	Prasugrel	Ticagrelor
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Clopidogrel	Prasugrel	Ticagrelor
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Due to the short reporting time of 4 hours, no adverse events took place during this time.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2014	Due to difficulties in recruitment to the prasugrel NSTEMI group, a substantial amendment was submitted and approved, REC ref no: 14/WM/1236

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported