Clinical trial results:
Antiplatelet effects of once versus twice daily dosing of aspirin after coronary artery bypass grafting

Summary

EudraCT number	2011-002233-19
Trial protocol	SE
Global end of trial date	01 July 2015

Results information

Result version number	v1 (current)
This version publication date	07 May 2021
First version publication date	07 May 2021

Trial information

Trial identification

Sponsor protocol code	ASA-CABG-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02482857
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Karolinska Institutet
Sponsor organisation address	17177, Stockholm, Sweden,
Public contact	Clinical Pharmacology Unit, Karolinska Institutet, 46 851775293, paul.hjemdahl@ki.se
Scientific contact	Clinical Pharmacology Unit, Karolinska Institutet, 46 851775293, paul.hjemdahl@ki.se

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	01 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2015
Global end of trial reached?	Yes
Global end of trial date	01 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to investigate the impact on platelet function of increasing either the aspirin dose (from 75 mg to 160 mg) or dosing frequency (to 75 mg BID) over 3 months in patients undergoing elective CABG surgery.

Protection of trial subjects:

he studywas approved by the Regional Ethical ReviewBoard in Stockholm(2011/1074-31/1). Patients are free to withdraw their consent for study treatment and/or consent to participate in the study at any time.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

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)	16
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from Karolinska University Hospital, Sweden, between December 2011 and July 2015.

Pre-assignment

Screening details:

Patients with stable angina pectoris scheduled to undergo elective CABG were screened. Exlusion criteria were intake of any other platelet inhibitor than ASA during the last seven days prior to surgery, known bleeding disorder or kidney failure, preoperative platelet count outside of the range 100,000–450,000/µL or a haemoglobin level below 80g/L.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ASA 75 mg OD

Arm description:

Patients were treated with ASA 75 mg once daily (OD) before the CABG surgery, and randomized to ASA 75 mg OD up to three months after the operation.

Arm type	Active comparator
Investigational medicinal product name	Aspirin
Investigational medicinal product code	11423 (for 75 mg)
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were treated with ASA 75 mg once daily (OD) before the CABG surgery, and randomized to ASA 75 mg OD up to three months after the operation.

Arm title	ASA 75 mg BID

Arm description:

Patients were treated with ASA 75 mg OD before the CABG surgery, and randomized to 75 mg twice daily (BID) up to three months after the operation.

Arm type	Experimental
Investigational medicinal product name	Aspirin
Investigational medicinal product code	11423 (for 75 mg)
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were treated with ASA 75 mg once daily (OD) before the CABG surgery, and randomized to 75 mg twice daily (BID) up to three months after the operation.

Arm title	ASA 160 mg OD

Arm description:

Patients were treated with ASA 75 mg once daily (OD) before the CABG surgery, and randomized to 160 mg OD up to three months after the operation.

Arm type	Experimental

Investigational medicinal product name	Aspirin
Investigational medicinal product code	11063 (for 160 mg)
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were treated with ASA 75 mg once daily (OD) before the CABG surgery, and randomized to ASA 160 mg OD up to three months after the operation.

Number of subjects in period 1	ASA 75 mg OD	ASA 75 mg BID	ASA 160 mg OD
Started	11	14	17
Completed	11	14	17

Baseline characteristics

Reporting groups	
Reporting group title	ASA 75 mg OD
Reporting group description:	
Patients were treated with ASA 75 mg once daily (OD) before the CABG surgery, and randomized to ASA 75 mg OD up to three months after the operation.	
Reporting group title	ASA 75 mg BID
Reporting group description:	
Patients were treated with ASA 75 mg OD before the CABG surgery, and randomized to 75 mg twice daily (BID) up to three months after the operation.	
Reporting group title	ASA 160 mg OD
Reporting group description:	
Patients were treated with ASA 75 mg once daily (OD) before the CABG surgery, and randomized to 160 mg OD up to three months after the operation.	

Reporting group values	ASA 75 mg OD	ASA 75 mg BID	ASA 160 mg OD
Number of subjects	11	14	17
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	69	66	67
standard deviation	± 10	± 7	± 11
Gender categorical Units: Subjects			
Female	1	0	0
Male	10	14	17
BMI Units: kg/m2			
arithmetic mean	27	29	27
standard deviation	± 3	± 3	± 2
Blood pressure Systolic Units: mm Hg			
arithmetic mean	131	133	143
standard deviation	± 15	± 20	± 17
Blood pressure Diastolic Units: mm Hg			
arithmetic mean	75	77	84

standard deviation	± 9	± 7	± 6
eGFR			
Estimated Glomerular filtration rate using the Cockroft and Gault equation			
Units: mL/min			
arithmetic mean	95	98	85
standard deviation	± 36	± 24	± 26
EuroSCORE II			
European System for Cardiac Operative Risk Evaluation Score II.			
Units: Percent			
median	2.5	1.7	2.4
full range (min-max)	0.9 to 8.6	0.9 to 4.6	0.9 to 10
History of smoking			
Units: Number (%)			
arithmetic mean	6	7	13
standard deviation	± 55	± 50	± 76
Hypertension			
Units: Numbers (%)			
arithmetic mean	8	14	9
standard deviation	± 73	± 100	± 53
Hyperlipidemia			
Units: Number (%)			
arithmetic mean	11	12	15
standard deviation	± 100	± 86	± 88
Diabetes mellitus			
Units: Number (%)			
arithmetic mean	4	3	4
standard deviation	± 36	± 21	± 24
Medication Beta blocker			
Units: Number (%)			
arithmetic mean	7	14	14
standard deviation	± 64	± 100	± 83
Medication ACE inhibitor			
angiotensin converting enzyme			
Units: Number (%)			
arithmetic mean	5	7	8
standard deviation	± 45	± 50	± 47
Medication Statin			
Units: Number (%)			
arithmetic mean	10	13	15
standard deviation	± 91	± 93	± 88
Haemoglobin			
Units: g/L			
arithmetic mean	139	141	135
full range (min-max)	115 to 159	133 to 151	108 to 150
White blood cell counts			
Units: Counts			
arithmetic mean	7	6	7
full range (min-max)	3.7 to 10.1	4.5 to 8.5	5.1 to 9.7
Platelet counts			
Units: Counts			
arithmetic mean	226	224	240
full range (min-max)	138 to 361	164 to 396	145 to 326

Mean platelet volume			
Units: Volume			
arithmetic mean	8	8	8
full range (min-max)	6.6 to 9.1	7.1 to 8.7	6.2 to 8.3

Reporting group values	Total		
Number of subjects	42		
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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	1		
Male	41		
BMI			
Units: kg/m2			
arithmetic mean			
standard deviation	-		
Blood pressure Systolic			
Units: mm Hg			
arithmetic mean			
standard deviation	-		
Blood pressure Diastolic			
Units: mm Hg			
arithmetic mean			
standard deviation	-		
eGFR			
Estimated Glomerular filtration rate using the Cockroft and Gault equation			
Units: mL/min			
arithmetic mean			
standard deviation	-		
EuroSCORE II			
European System for Cardiac Operative Risk Evaluation Score II.			
Units: Percent			
median			
full range (min-max)	-		
History of smoking			
Units: Number (%)			

arithmetic mean standard deviation	-		
Hypertension Units: Numbers (%) arithmetic mean standard deviation	-		
Hyperlipidemia Units: Number (%) arithmetic mean standard deviation	-		
Diabetes mellitus Units: Number (%) arithmetic mean standard deviation	-		
Medication Beta blocker Units: Number (%) arithmetic mean standard deviation	-		
Medication ACE inhibitor			
angiotensin converting enzyme			
Units: Number (%) arithmetic mean standard deviation	-		
Medication Statin Units: Number (%) arithmetic mean standard deviation	-		
Haemoglobin Units: g/L arithmetic mean full range (min-max)	-		
White blood cell counts Units: Counts arithmetic mean full range (min-max)	-		
Platelet counts Units: Counts arithmetic mean full range (min-max)	-		
Mean platelet volume Units: Volume arithmetic mean full range (min-max)	-		

End points

End points reporting groups

Reporting group title	ASA 75 mg OD
Reporting group description:	
Patients were treated with ASA 75 mg once daily (OD) before the CABG surgery, and randomized to ASA 75 mg OD up to three months after the operation.	
Reporting group title	ASA 75 mg BID
Reporting group description:	
Patients were treated with ASA 75 mg OD before the CABG surgery, and randomized to 75 mg twice daily (BID) up to three months after the operation.	
Reporting group title	ASA 160 mg OD
Reporting group description:	
Patients were treated with ASA 75 mg once daily (OD) before the CABG surgery, and randomized to 160 mg OD up to three months after the operation.	

Primary: Haemoglobin at postop

End point title	Haemoglobin at postop
End point description:	
End point type	Primary
End point timeframe:	
Haemoglobin at discharge (postop) and 1 and 3 months after the operation in patients receiving three dosages of ASA (75 mg OD, 75 mg BID and 160 OD) after discharge.	

End point values	ASA 75 mg OD	ASA 75 mg BID	ASA 160 mg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	14	17	
Units: g/L				
arithmetic mean (full range (min-max))				
Postop	103 (85 to 114)	101 (84 to 115)	99 (82 to 115)	
1 month	120 (92 to 136)	125 (113 to 136)	117 (98 to 132)	
3 months	136 (110 to 156)	138 (118 to 147)	131 (106 to 148)	

Statistical analyses

Statistical analysis title	Difference Haemoglobin
Statistical analysis description:	
Differences in haemoglobin for within-group differences, compared to preoperative baseline, at discharge (postop) 1- and 3-months postop.	
Comparison groups	ASA 75 mg OD v ASA 75 mg BID v ASA 160 mg OD

Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANOVA

Primary: White blood cell counts at postop

End point title	White blood cell counts at postop

End point description:

End point type	Primary

End point timeframe:

White blood cell counts at discharge (postop) and 1 and 3 months after the operation in patients receiving three dosages of ASA (75 mg OD, 75 mg BID and 160 OD) after discharge.

End point values	ASA 75 mg OD	ASA 75 mg BID	ASA 160 mg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	14	17	
Units: 10(6)/L				
arithmetic mean (full range (min-max))				
Postop	10 (5.5 to 15.4)	9 (6.4 to 11.0)	10 (4.3 to 13.6)	
1 month	8 (5.5 to 9.9)	7 (4.9 to 9.8)	8 (5.7 to 9.5)	
3 months	7 (4.0 to 9.9)	6 (4.5 to 9.5)	7 (5.4 to 8.3)	

Statistical analyses

Statistical analysis title	Difference White blood cell counts

Statistical analysis description:

Differences in white blood cell counts for within-group differences, compared to preoperative baseline, at discharge (postop) 1- and 3-months postop.

Comparison groups	ASA 75 mg OD v ASA 75 mg BID v ASA 160 mg OD
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANOVA

Primary: Platelet counts at postop

End point title	Platelet counts at postop

End point description:

End point type	Primary

End point timeframe:

Platelet counts at discharge (postop) and 1 and 3 months after the operation in patients receiving three dosages of ASA (75 mg OD, 75 mg BID and 160 OD) after discharge.

End point values	ASA 75 mg OD	ASA 75 mg BID	ASA 160 mg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	14	17	
Units: 10(9)/L				
arithmetic mean (full range (min-max))				
Postop	237 (165 to 321)	210 (147 to 279)	217 (130 to 348)	
1 month	314 (233 to 394)	246 (180 to 338)	310 (197 to 461)	
3 months	256 (157 to 362)	212 (156 to 264)	238 (164 to 301)	

Statistical analyses

Statistical analysis title	Difference Platelet counts

Statistical analysis description:

Differences in platelet counts for within-group differences, compared to preoperative baseline, at discharge (postop) 1- and 3-months postop.

Comparison groups	ASA 75 mg OD v ASA 75 mg BID v ASA 160 mg OD
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANOVA

Primary: Mean platelet volume at postop

End point title	Mean platelet volume at postop

End point description:

End point type	Primary

End point timeframe:

Mean platelet volume at discharge (postop) and 1 and 3 months after the operation in patients receiving three dosages of ASA (75 mg OD, 75 mg BID and 160 OD) after discharge.

End point values	ASA 75 mg OD	ASA 75 mg BID	ASA 160 mg OD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	14	17	
Units: fL				
arithmetic mean (full range (min-max))				
Postop	8 (6.6 to 9.0)	8 (6.8 to 8.6)	8 (6.5 to 9.0)	
1 month	8 (6.7 to 9.2)	8 (6.6 to 8.5)	8 (6.2 to 8.8)	
3 month	8 (6.7 to 9.7)	8 (6.8 to 8.8)	8 (6.5 to 9.0)	

Statistical analyses

Statistical analysis title	Difference Mean platelet volume

Statistical analysis description:

Differences in mean platelet volumen for within-group differences, compared to preoperative baseline, at discharge (postop) 1- and 3-months postop.

Comparison groups	ASA 75 mg OD v ASA 75 mg BID v ASA 160 mg OD
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to study completion at 3 months postop.	
Adverse event reporting additional description:	
Systematic collection of adverse events at the hospital, no special dictionary was used.	
Assessment type	Systematic

Dictionary used	
Dictionary name	See AE-description
Dictionary version	n/a

Reporting groups	
Reporting group title	ASA 75 mg OD
Reporting group description:	
Patients were treated with ASA 75 mg once daily (OD) before the CABG surgery, and randomized to ASA 75 mg OD up to three months after the operation.	
Reporting group title	ASA 75 mg BID
Reporting group description:	
Patients were treated with ASA 75 mg OD before the CABG surgery, and randomized to 75 mg twice daily (BID) up to three months after the operation.	
Reporting group title	ASA 160 mg OD
Reporting group description:	
Patients were treated with ASA 75 mg once daily (OD) before the CABG surgery, and randomized to 160 mg OD up to three months after the operation.	

Serious adverse events	ASA 75 mg OD	ASA 75 mg BID	ASA 160 mg OD
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 14 (0.00%)	0 / 17 (0.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	ASA 75 mg OD	ASA 75 mg BID	ASA 160 mg OD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 11 (18.18%)	4 / 14 (28.57%)	4 / 17 (23.53%)
Blood and lymphatic system disorders			
slight nose bleed, mouth bleeding associated with tooth brushing or bruises	Additional description: One patient with insulin-treated diabetes mellitus and advanced three-vessel disease treated with ASA 160 mg once daily died suddenly two months after the operation, but the death was not associated with the treatment/study.		
subjects affected / exposed	2 / 11 (18.18%)	4 / 14 (28.57%)	4 / 17 (23.53%)
occurrences (all)	2	4	4

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.

Therewas un unfortunate high dropout of initially included patients, we encountered considerable difficulties in obtaining accurate blood samples on all four occasions during the 3m follow-up in several patients.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27907814