Clinical trial results:
Bivalirudin versus Heparin in NST and ST-Evaluation myocardial infarction in patients on modern antiplatelet therapy in SWEDEHEART (the VALIDATE-SWEDEHEART-trial)

Summary

EudraCT number	2012-005260-10
Trial protocol	SE
Global end of trial date	10 March 2017

Results information

Result version number	v1 (current)
This version publication date	13 February 2019
First version publication date	13 February 2019

Trial information

Trial identification

Sponsor protocol code	U-2013-028

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Uppsala Clinical Research Center (UCR)
Sponsor organisation address	Dag Hammarskjölds väg 38, Uppsala, Sweden, 751 85
Public contact	Jonas Oldgren, Uppsala Clinical Research Center, +46 18 611 2765, jonas.oldgren@ucr.uu.se
Scientific contact	David Erlinge, Skåne University Hospital, Department of Cardiology, +46 46 172597, david.erlinge@med.lu.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	10 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 March 2017
Global end of trial reached?	Yes
Global end of trial date	10 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare all-cause death, MI, and bleeding events in patients with STEMI and NSTEMI at 180 days, treated with PCI and either Bivalirudin infusion or Heparin i.v. according to local protocol.

Protection of trial subjects:

An independent Data Safety Monitoring Board (DSMB) (sometimes referred to as a Data Safety Monitoring Committee (DSMC)) is responsible for safeguarding the interest of trial participants, assessing the safety of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. This committee is also responsible for making recommendations to the study leadership to continue or terminate the trial with regard to safety considerations based on reports provided by an unblinded statistician.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 June 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 6006
Worldwide total number of subjects	6006
EEA total number of subjects	6006

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)	2327

From 65 to 84 years	3362
85 years and over	317

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were recruited among those referred to the centers for PCI because of STEMI or NSTEMI. NSTEMI patients provided written consent before angiography, while STEMI patients first gave a witnessed consent before diagnostic coronary angiography in the catheterization lab followed by signing informed consent within 48h if they wished to continue.

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	Heparin-STEMI

Arm description:

Treatment with heparin i.v. alone (according to local practice) in patients with ST-elevation myocardial infarction (STEMI) treated with bolus dose of potent P2Y12 receptor inhibitors; ticagrelor, prasugrel or cangrelor before start of PCI.

Arm type	Active comparator
Investigational medicinal product name	Heparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Injection
Routes of administration	Intraarterial use, Intravenous bolus use

Dosage and administration details:

The control group received treatment with unfractionated heparin. Heparin was administered as an intravenous or intra-arterial bolus according to local practice. A dose of 70-100U/kg was recommended.

Arm title	Bivalirudin-STEMI

Arm description:

Treatment with Bivalirudin 0.75 mg/kg followed by an infusion of 1.75 mg per kilogram per hour in patients with ST-elevation myocardial infarction (STEMI) treated with bolus dose of potent P2Y12 receptor inhibitors; ticagrelor, prasugrel or cangrelor before start of PCI.

Arm type	Experimental
Investigational medicinal product name	Bivalirudin
Investigational medicinal product code	
Other name	Angiox
Pharmaceutical forms	Infusion, Injection
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

Bivalirudin 0.75 mg/kg followed by an infusion of 1.75 mg per kilogram per hour (optional to add up to 3000U heparin in lab or up to 5000U given pre-hospital).

Arm title	Heparin-NSTEMI

Arm description:

Treatment with heparin i.v. alone (according to local practice) in patients with non-ST-elevation myocardial infarction (NSTEMI) treated with bolus dose of potent P2Y12 receptor inhibitors; ticagrelor, prasugrel or cangrelor before start of PCI.

Arm type	Active comparator

Investigational medicinal product name	Heparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Injection
Routes of administration	Intraarterial use, Intravenous bolus use

Dosage and administration details:

The control group received treatment with unfractionated heparin. Heparin was administered as an intravenous or intra-arterial bolus according to local practice. A dose of 70-100U/kg was recommended.

Arm title	Bivalirudin-NSTEMI

Arm description:

Treatment with Bivalirudin 0.75 mg/kg followed by an infusion of 1.75 mg per kilogram per hour in patients with non-ST-elevation myocardial infarction (NSTEMI) treated with bolus dose of potent P2Y12 receptor inhibitors; ticagrelor, prasugrel or cangrelor before start of PCI.

Arm type	Experimental
Investigational medicinal product name	Bivalirudin
Investigational medicinal product code	
Other name	Angiox
Pharmaceutical forms	Infusion, Injection
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

Bivalirudin 0.75 mg/kg followed by an infusion of 1.75 mg per kilogram per hour (optional to add up to 3000U heparin in lab or up to 5000U given pre-hospital).

Number of subjects in period 1	Heparin-STEMI	Bivalirudin-STEMI	Heparin-NSTEMI
Started	1504	1501	1498
Completed	1489	1482	1479
Not completed	15	19	19
Consent withdrawn by subject	11	12	14
Lost to follow-up	4	7	5

Number of subjects in period 1	Bivalirudin-NSTEMI
Started	1503
Completed	1488
Not completed	15
Consent withdrawn by subject	12
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	Heparin-STEMI
Reporting group description:	
Treatment with heparin i.v. alone (according to local practice) in patients with ST-elevation myocardial infarction (STEMI) treated with bolus dose of potent P2Y12 receptor inhibitors; ticagrelor, prasugrel or cangrelor before start of PCI.	
Reporting group title	Bivalirudin-STEMI
Reporting group description:	
Treatment with Bivalirudin 0.75 mg/kg followed by an infusion of 1.75 mg per kilogram per hour in patients with ST-elevation myocardial infarction (STEMI) treated with bolus dose of potent P2Y12 receptor inhibitors; ticagrelor, prasugrel or cangrelor before start of PCI.	
Reporting group title	Heparin-NSTEMI
Reporting group description:	
Treatment with heparin i.v. alone (according to local practice) in patients with non-ST-elevation myocardial infarction (NSTEMI) treated with bolus dose of potent P2Y12 receptor inhibitors; ticagrelor, prasugrel or cangrelor before start of PCI.	
Reporting group title	Bivalirudin-NSTEMI
Reporting group description:	
Treatment with Bivalirudin 0.75 mg/kg followed by an infusion of 1.75 mg per kilogram per hour in patients with non-ST-elevation myocardial infarction (NSTEMI) treated with bolus dose of potent P2Y12 receptor inhibitors; ticagrelor, prasugrel or cangrelor before start of PCI.	

Reporting group values	Heparin-STEMI	Bivalirudin-STEMI	Heparin-NSTEMI
Number of subjects	1504	1501	1498
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	67.0	66.6	67.6
standard deviation	± 10.9	± 11.4	± 11.0
Gender categorical Units: Subjects			
Female	417	407	404
Male	1086	1090	1091
No data	1	4	3
Smoking Units: Subjects			
Never	604	589	581
Ex smoker >1 month	428	446	592

Smoker	419	417	291
Unknown	52	45	31
No data	1	4	3
BMI (kg/m2)			
Units: kg/m2			
arithmetic mean	27.2	27.3	27.7
standard deviation	± 5.3	± 5.3	± 4.4
Weight (kg)			
Units: kg			
arithmetic mean	82.2	82.4	83.6
standard deviation	± 15.5	± 15.7	± 15.8

Reporting group values	Bivalirudin-NSTEMI	Total	
Number of subjects	1503	6006	
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	67.6		
standard deviation	± 10.7	-	
Gender categorical			
Units: Subjects			
Female	364	1592	
Male	1139	4406	
No data	0	8	
Smoking			
Units: Subjects			
Never	593	2367	
Ex smoker >1 month	581	2047	
Smoker	299	1426	
Unknown	30	158	
No data	0	8	
BMI (kg/m2)			
Units: kg/m2			
arithmetic mean	27.7		
standard deviation	± 7.2	-	
Weight (kg)			
Units: kg			
arithmetic mean	83.7		
standard deviation	± 16.3	-	

Subject analysis sets	
Subject analysis set title	Heparin-STEMI (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population is defined as any patient with data who was intentionally randomized.	
Subject analysis set title	Bivalirudin-STEMI (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population is defined as any patient with data who was intentionally randomized.	
Subject analysis set title	Heparin-NSTEMI (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population is defined as any patient with data who was intentionally randomized.	
Subject analysis set title	Bivalirudin-NSTEMI (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population is defined as any patient with data who was intentionally randomized.	
Subject analysis set title	Heparin (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population is defined as any patient with data who was intentionally randomized.	
Subject analysis set title	Bivalirudin (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population is defined as any patient with data who was intentionally randomized.	

Reporting group values	Heparin-STEMI (ITT)	Bivalirudin-STEMI (ITT)	Heparin-NSTEMI (ITT)
Number of subjects	1504	1501	1498
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	67.0	66.6	67.6
standard deviation	± 10.9	± 11.4	± 11.0
Gender categorical Units: Subjects			
Female	417	407	404
Male	1086	1090	1091
No data	1	4	3

Smoking Units: Subjects			
Never	604	589	581
Ex smoker >1 month	428	446	592
Smoker	419	417	291
Unknown	52	45	31
No data	1	4	3
BMI (kg/m2) Units: kg/m2			
arithmetic mean	27.2	27.3	27.7
standard deviation	± 5.3	± 5.3	± 4.4
Weight (kg) Units: kg			
arithmetic mean	82.2	82.4	83.6
standard deviation	± 15.5	± 15.7	± 15.8

Reporting group values	Bivalirudin-NSTEMI (ITT)	Heparin (ITT)	Bivalirudin (ITT)
Number of subjects	1503	3002	3004
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	67.6	67.3	67.1
standard deviation	± 10.7	± 11.0	± 11.1
Gender categorical Units: Subjects			
Female	364	821	771
Male	1139	2177	2229
No data	0	4	4
Smoking Units: Subjects			
Never	593	1185	1182
Ex smoker >1 month	581	1020	1027
Smoker	299	710	716
Unknown	30	83	75
No data	0	4	4
BMI (kg/m2) Units: kg/m2			
arithmetic mean	27.7	27.5	27.5
standard deviation	± 7.2	± 4.8	± 6.4
Weight (kg)			

Units: kg			
arithmetic mean	83.7	82.9	83.1
standard deviation	± 16.3	± 15.7	± 16.0

End points

End points reporting groups

Reporting group title	Heparin-STEMI
Reporting group description:	
Treatment with heparin i.v. alone (according to local practice) in patients with ST-elevation myocardial infarction (STEMI) treated with bolus dose of potent P2Y12 receptor inhibitors; ticagrelor, prasugrel or cangrelor before start of PCI.	
Reporting group title	Bivalirudin-STEMI
Reporting group description:	
Treatment with Bivalirudin 0.75 mg/kg followed by an infusion of 1.75 mg per kilogram per hour in patients with ST-elevation myocardial infarction (STEMI) treated with bolus dose of potent P2Y12 receptor inhibitors; ticagrelor, prasugrel or cangrelor before start of PCI.	
Reporting group title	Heparin-NSTEMI
Reporting group description:	
Treatment with heparin i.v. alone (according to local practice) in patients with non-ST-elevation myocardial infarction (NSTEMI) treated with bolus dose of potent P2Y12 receptor inhibitors; ticagrelor, prasugrel or cangrelor before start of PCI.	
Reporting group title	Bivalirudin-NSTEMI
Reporting group description:	
Treatment with Bivalirudin 0.75 mg/kg followed by an infusion of 1.75 mg per kilogram per hour in patients with non-ST-elevation myocardial infarction (NSTEMI) treated with bolus dose of potent P2Y12 receptor inhibitors; ticagrelor, prasugrel or cangrelor before start of PCI.	
Subject analysis set title	Heparin-STEMI (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population is defined as any patient with data who was intentionally randomized.	
Subject analysis set title	Bivalirudin-STEMI (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population is defined as any patient with data who was intentionally randomized.	
Subject analysis set title	Heparin-NSTEMI (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population is defined as any patient with data who was intentionally randomized.	
Subject analysis set title	Bivalirudin-NSTEMI (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population is defined as any patient with data who was intentionally randomized.	
Subject analysis set title	Heparin (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population is defined as any patient with data who was intentionally randomized.	
Subject analysis set title	Bivalirudin (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population is defined as any patient with data who was intentionally randomized.	

Primary: Difference in all-cause death, myocardial infarction, or major bleeding events in patients with STEMI and NSTEMI at 180 days, treated with PCI and either Bivalirudin infusion or Heparin i.v. according to local protocol.

End point title	Difference in all-cause death, myocardial infarction, or major bleeding events in patients with STEMI and NSTEMI at 180 days, treated with PCI and either Bivalirudin infusion or

	Heparin i.v. according to local protocol.

End point description:

Events were followed up using SWEDEHEART and other national registries and telephone contact at 7 and 180 days from randomization. Patients without events were censored on day 180 for derived 180 day completers, and recorded day of discontinuation for other patients. A Clinical Endpoint Committee (CEC) was established to perform an independent adjudication for all reported primary endpoints.

End point type	Primary

End point timeframe:

Follow up of primary endpoints was performed by telephone contact with the patients or first-degree relatives by a nurse 7 days and 180 days after randomization.

End point values	Heparin-STEMI (ITT)	Bivalirudin-STEMI (ITT)	Heparin-NSTEMI (ITT)	Bivalirudin-NSTEMI (ITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1504	1501	1498	1503
Units: Events	196	187	187	182

End point values	Heparin (ITT)	Bivalirudin (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3002	3004		
Units: Events	383	369		

Statistical analyses

Statistical analysis title	Analysis of difference of primary endpoint

Statistical analysis description:

The hazard ratio between the bivalirudin group and the heparin group was estimated, in the ITT population, using a Cox proportional hazard model with factor randomized treatment, and presented with a 95% confidence interval. The protocol pre-defines the log-rank test, hence the equivalent score test p-value from the Cox model was used. A two-sided p-value of <0.05 is regarded as statistically significant.

Comparison groups	Heparin (ITT) v Bivalirudin (ITT)
Number of subjects included in analysis	6006
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.5362
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.1

Notes:

[1] - 12.3% patients (369 of 3004) in the bivalirudin group and in 12.8% (383 of 3002) in the heparin group (hazard ratio, 0.96; 95% confidence interval [CI], 0.83 to 1.10; P = 0.5362).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Registration of adverse events started at visit 1 (day 0) after informed consent and when treatment with study medication had been given and went on until day 7 after randomization into the study.

Adverse event reporting additional description:

The following events were not collected as AE: suspected primary events or stroke, symptoms or worsening of STEMI/NSTEMI, common events in patients undergoing PCI, hospitalization in connection with PCI or planned hospitalizations, and expected AEs to heparin or bivalirudin.

Assessment type	Systematic

Dictionary used

Dictionary name	ICD-10-SE
Dictionary version	2011

Reporting groups

Reporting group title	Heparin

Reporting group description:

Treatment with heparin i.v. alone (according to local practice) in patients with STEMI and NSTEMI treated with bolus dose of potent P2Y12 receptor inhibitors; ticagrelor, prasugrel or cangrelor before start of PCI.

Reporting group title	Bivalirudin

Reporting group description:

Treatment with Bivalirudin 0.75 mg/kg followed by an infusion of 1.75 mg per kilogram per hour in patients with STEMI and NSTEMI treated with bolus dose of potent P2Y12 receptor inhibitors; ticagrelor, prasugrel or cangrelor before start of PCI.

Serious adverse events	Heparin	Bivalirudin	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 3002 (0.60%)	11 / 3004 (0.37%)	
number of deaths (all causes)	84	88	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm of colon, unspecified			
subjects affected / exposed	1 / 3002 (0.03%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of gallbladder			
subjects affected / exposed	1 / 3002 (0.03%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of bronchus and lung			

subjects affected / exposed	1 / 3002 (0.03%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of brain, Cerebral ventricle			
subjects affected / exposed	0 / 3002 (0.00%)	1 / 3004 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary and unspecified malignant neoplasm of lymph nodes, Intra-abdominal lymph nodes			
subjects affected / exposed	1 / 3002 (0.03%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary malignant neoplasm of bone and bone marrow			
subjects affected / exposed	1 / 3002 (0.03%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 3002 (0.03%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 3002 (0.03%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
General disorders and administration site conditions			
Malaise and fatigue			
subjects affected / exposed	0 / 3002 (0.00%)	1 / 3004 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unspecified adverse effect of drug or medicament			

subjects affected / exposed	0 / 3002 (0.00%)	1 / 3004 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis due to aspiration of blood			
subjects affected / exposed	1 / 3002 (0.03%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Postprocedural renal failure			
subjects affected / exposed	0 / 3002 (0.00%)	1 / 3004 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Intracardiac thrombosis, not elsewhere classified			
subjects affected / exposed	3 / 3002 (0.10%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest, unspecified			
subjects affected / exposed	2 / 3002 (0.07%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 3002 (0.03%)	1 / 3004 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope and collapse			
subjects affected / exposed	1 / 3002 (0.03%)	1 / 3004 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion (noninflammatory)			

subjects affected / exposed	1 / 3002 (0.03%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with complex part			
subjects affected / exposed	1 / 3002 (0.03%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient cerebral ischaemic attack, unspecified			
subjects affected / exposed	0 / 3002 (0.00%)	1 / 3004 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vestibular neuronitis			
subjects affected / exposed	1 / 3002 (0.03%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Central retinal artery occlusion			
subjects affected / exposed	0 / 3002 (0.00%)	1 / 3004 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus, unspecified			
subjects affected / exposed	1 / 3002 (0.03%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular disease of intestine, part unspecified, without perforation or abscess			
subjects affected / exposed	1 / 3002 (0.03%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pancreatitis, unspecified			

subjects affected / exposed	1 / 3002 (0.03%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Chronic cholecystitis			
subjects affected / exposed	1 / 3002 (0.03%)	0 / 3004 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cutaneous abscess, furuncle and carbuncle, unspecified			
subjects affected / exposed	0 / 3002 (0.00%)	1 / 3004 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis and colitis of unspecified origin			
subjects affected / exposed	0 / 3002 (0.00%)	1 / 3004 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia, unspecified			
subjects affected / exposed	0 / 3002 (0.00%)	1 / 3004 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.09 %

Non-serious adverse events	Heparin	Bivalirudin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 3002 (0.57%)	19 / 3004 (0.63%)	
General disorders and administration site conditions			
Dyspnoea			
subjects affected / exposed	2 / 3002 (0.07%)	3 / 3004 (0.10%)	
occurrences (all)	2	3	
Gastrointestinal disorders			

Change in bowel habit subjects affected / exposed occurrences (all)	4 / 3002 (0.13%) 4	5 / 3004 (0.17%) 5	
Skin and subcutaneous tissue disorders Urticaria, unspecified subjects affected / exposed occurrences (all)	4 / 3002 (0.13%) 4	4 / 3004 (0.13%) 4	
Rash and other nonspecific skin eruption subjects affected / exposed occurrences (all)	1 / 3002 (0.03%) 1	3 / 3004 (0.10%) 3	
Endocrine disorders Unspecified diabetes mellitus subjects affected / exposed occurrences (all)	3 / 3002 (0.10%) 3	4 / 3004 (0.13%) 4	
Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	3 / 3002 (0.10%) 3	0 / 3004 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 January 2013	Amendment 1 included minor administrative changes to the protocol.
15 February 2014	Amendment 3 included minor administrative changes to the protocol. Note that Amendment 2 was rejected by the regulatory authority and was not implemented.
17 October 2014	In Amendment 4, the following secondary outcome variables were added: • The primary endpoint combined with stroke (added post-FPI, Amendment IV, 2014-10-17) • Bail-out use of GpIIb/IIIa inhibitors during PCI (added post-FPI, Amendment IV, 2014-10-17)
06 July 2015	In Amendment 5, the following secondary outcome variable was updated : • Time to subtypes of reinfarction as reported in by CEC (1, 2, 3, 4a, 4b, 5). (Added post-FPI, Amendment V, 2015-07-06, although adjudication of infarction types was planned in the first version of the Clinical Endpoint Committee (CEC) Charter (dated 2014-12-18), the protocol, by mistake, states time to "rehospitalization with" subtypes of myocardial infarction (MI), but the CEC does not adjudicate rehospitalization, only MI).

Notes:

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.

Note that age data is missing for 7 patients. In the results reported for "Subjects enrolled per age group", these patients are included in the most common age group (Adults 65-84y).

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28844201