Clinical trial results:
RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF 6 MONTHS VERSUS 12 MONTHS CLOPIDOGREL THERAPY AFTER DRUG-ELUTING STENT IMPLANTATION - INTRACORONARY STENTING AND ANTITHROMBOTIC REGIMEN: SAFETY AND EFFICACY OF SIX MONTHS DUAL ANTIPLATELET THERAPY AFTER DRUG-ELUTING STENTING – ISAR-SAFE

Summary

EudraCT number	2007-006263-68
Trial protocol	DE AT DK
Global end of trial date	23 January 2015

Results information

Result version number	v1 (current)
This version publication date	29 April 2022
First version publication date	29 April 2022
Summary attachment (see zip file)	Publication_ISAR-SAFE_2007-006263-68_eurheartj.ehu523.full (ISAR-SAFE_2007-006263-68_eurheartj.ehu523.full.pdf)

Trial information

Trial identification

Sponsor protocol code	GE IDE No. A01207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00661206
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	German Heart Centre Munich
Sponsor organisation address	Lazarettstr. 36, Munich, Germany, 80636
Public contact	Prof. Dr. Adnan Kastrati, German Heart Centre Munich, 0049 89 1218 4578, kastrati@dhm.mhn.de
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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	23 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 January 2015
Global end of trial reached?	Yes
Global end of trial date	23 January 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The hypothesis to be tested is whether clopidogrel therapy duration of 6 months after DES implantation is non-inferior to a 12 month therapy in terms of clinical outcomes (composite of death, myocardial infarction, definite or probable stent thrombosis according to Academic Research Consortium, stroke or TIMI major bleeding; non-inferiority hypothesis).
The primary end point of the study is a composite of death, myocardial infarction, stent thrombosis (definite or probable - according to Academic Research Consortium [ARC] criteria), stroke or TIMI major bleeding at 9 months after randomization.

Protection of trial subjects:

Not applicable.

Background therapy:

Patients received clopidogrel therapy for 6 months after drug-eluting stent implantation due to symptoms or signs of coronary artery disease.

Evidence for comparator:

No comparators used.

Actual start date of recruitment	01 October 2008
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	Germany: 2898
Country: Number of subjects enrolled	Albania: 3
Country: Number of subjects enrolled	Austria: 43
Country: Number of subjects enrolled	Belgium: 221
Country: Number of subjects enrolled	China: 221
Country: Number of subjects enrolled	Denmark: 147
Country: Number of subjects enrolled	Ireland: 17
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Japan: 49
Country: Number of subjects enrolled	Netherlands: 292
Country: Number of subjects enrolled	New Zealand: 26
Country: Number of subjects enrolled	Switzerland: 43
Country: Number of subjects enrolled	United States: 31

Worldwide total number of subjects	4005
EEA total number of subjects	3632

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)	1761
From 65 to 84 years	2189
85 years and over	55

Subject disposition

Recruitment

Recruitment details:

Patients on clopidogrel therapy at 6 months (- 1/+2 months) after DES implantation and meeting the inclusion criteria were considered candidates for participation in the study. They have been randomized to an additional 6 month period of clopidogrel or placebo. The recruitment took place worldwide from Oct 2008 to Apr 2014.

Pre-assignment

Screening details:

Inclusion Criteria:
1) Patients on clopidogrel therapy at 6 months (-1/+2 months) after DES implantation
2) Informed, written consent
3) Men and women aged ≥ 18 years

Pre-assignment period milestones

Number of subjects started	4005
Number of subjects completed	4005

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Tablets with an identical appearance have been used for both treatment groups (clopidogrel or placebo).

Arms

Are arms mutually exclusive?	Yes
Arm title	Clopidogrel

Arm description:

Patients on clopidogrel therapy at 6 months (-1/+2 months) after DES implantation and meeting the inclusion criteria have been randomized to an additional 6 months period of clopidogrel therapy.

Arm type	Experimental
Investigational medicinal product name	Plavix 75 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral intake of 1 tablet (75 mg clopidogrel) daily for a period of 6 months (six sealed plastic bottles with 30 clopidogrel tablets)

Arm title	Placebo

Arm description:

Patients who received clopidogrel therapy 6 months (-1/+2 months) after DES implantation and met the inclusion criteria were randomly assigned to a 6 months period of placebo therapy.

Arm type	Placebo

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

Dosage and administration details:

Oral intake of 1 tablet daily for a period of 6 months

Number of subjects in period 1	Clopidogrel	Placebo
Started	2007	1998
Completed	2003	1997
Not completed	4	1
Consent withdrawn by subject	4	1

Baseline characteristics

Reporting groups	
Reporting group title	Clopidogrel
Reporting group description:	
Patients on clopidogrel therapy at 6 months (-1/+2 months) after DES implantation and meeting the inclusion criteria have been randomized to an additional 6 months period of clopidogrel therapy.	
Reporting group title	Placebo
Reporting group description:	
Patients who received clopidogrel therapy 6 months (-1/+2 months) after DES implantation and met the inclusion criteria were randomly assigned to a 6 months period of placebo therapy.	

Reporting group values	Clopidogrel	Placebo	Total
Number of subjects	2007	1998	4005
Age categorical Units: Subjects			
Adults (18-64 years)	884	877	1761
From 65-84 years	1098	1091	2189
85 years and over	25	30	55
Gender categorical Units: Subjects			
Female	391	386	777
Male	1616	1612	3228
Arterial hypertension Units: Subjects			
Arterial hypertension yes	1830	1797	3627
Arterial hypertension no	177	201	378
Hypercholesterolaemia Units: Subjects			
Hypercholesterolaemia yes	1748	1747	3495
Hypercholesterolaemia no	259	251	510
Diabetis mellitus Units: Subjects			
Diabetis mellitus yes	484	495	979
Diabetis mellitus no	1523	1503	3026
Family history Units: Subjects			
Family history yes	680	707	1387
Family history no	1327	1291	2618
Smoking status Units: Subjects			
Smoking status yes	1025	995	2020
Smoking status no	982	1003	1985
History of prior myocardial infarction Units: Subjects			
History of prior myocardial infarction yes	491	516	1007
History of prior myocardial infarction no	1516	1482	2998
History of prior coronary artery bypass			

graft Units: Subjects			
History of prior coronary artery bypass graft yes	149	152	301
History of prior coronary artery bypass graft no	1858	1846	3704
Body mass index Units: kg/m²			
median	27.5	27.2	
inter-quartile range (Q1-Q3)	24.9 to 30.4	24.9 to 30.1	-

Subject analysis sets

Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The full analysis set included 4000 patients. 5 patients have withdrawn their consent immediately or were excluded by the treating physician before taking any study medication and were not included in the final analysis.

Reporting group values	Intention-to-treat		
Number of subjects	4000		
Age categorical Units: Subjects			
Adults (18-64 years)	1760		
From 65-84 years	2185		
85 years and over	55		
Gender categorical Units: Subjects			
Female	777		
Male	3223		
Arterial hypertension Units: Subjects			
Arterial hypertension yes	3627		
Arterial hypertension no	373		
Hypercholesterolaemia Units: Subjects			
Hypercholesterolaemia yes	3495		
Hypercholesterolaemia no	505		
Diabetis mellitus Units: Subjects			
Diabetis mellitus yes	979		
Diabetis mellitus no	3021		
Family history Units: Subjects			
Family history yes	1387		
Family history no	2613		
Smoking status Units: Subjects			
Smoking status yes	2020		
Smoking status no	1980		
History of prior myocardial infarction			

Units: Subjects			
History of prior myocardial infarction yes	1007		
History of prior myocardial infarction no	2993		
History of prior coronary artery bypass graft Units: Subjects			
History of prior coronary artery bypass graft yes	301		
History of prior coronary artery bypass graft no	3699		
Body mass index Units: kg/m² median inter-quartile range (Q1-Q3)			

End points

End points reporting groups

Reporting group title	Clopidogrel
Reporting group description:	
Patients on clopidogrel therapy at 6 months (-1/+2 months) after DES implantation and meeting the inclusion criteria have been randomized to an additional 6 months period of clopidogrel therapy.	
Reporting group title	Placebo
Reporting group description:	
Patients who received clopidogrel therapy 6 months (-1/+2 months) after DES implantation and met the inclusion criteria were randomly assigned to a 6 months period of placebo therapy.	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The full analysis set included 4000 patients. 5 patients have withdrawn their consent immediately or were excluded by the treating physician before taking any study medication and were not included in the final analysis.	

Primary: Primary: A composite end point of death, myocardial infarction, stent thrombosis (definite or probable), stroke, or thrombolysis in myocardial infarction (TIMI) major bleeding

End point title	Primary: A composite end point of death, myocardial infarction, stent thrombosis (definite or probable), stroke, or thrombolysis in myocardial infarction (TIMI) major bleeding
End point description:	
composite of death, myocardial infarction, stent thrombosis (definite or probable), stroke, or thrombolysis in myocardial infarction (TIMI) major bleeding	
End point type	Primary
End point timeframe:	
at 9 months after randomization, i.e. 15 months after the index intervention	

End point values	Clopidogrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2003	1997		
Units: Patients	32	29		

Statistical analyses

Statistical analysis title	Primary endpoint analysis
Comparison groups	Clopidogrel v Placebo
Number of subjects included in analysis	4000
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.05
Method	Chi-squared
Parameter estimate	Median difference (final values)
Point estimate	-0.001

Confidence interval	
level	95 %
sides	1-sided
upper limit	0.006

Secondary: Secondary: Death	
End point title	Secondary: Death
End point description:	
End point type	Secondary
End point timeframe:	
at 9 months after randomization, i.e. 15 months after the index intervention	

End point values	Clopidogrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2003	1997		
Units: Patients	12	8		

Statistical analyses

Statistical analysis title	Secondary endpoint: death
Comparison groups	Clopidogrel v Placebo
Number of subjects included in analysis	4000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.63

Secondary: Secondary: Definite stent thrombosis	
End point title	Secondary: Definite stent thrombosis
End point description:	
End point type	Secondary

End point timeframe:
at 9 months after randomization, i.e. 15 months after the index intervention

End point values	Clopidogrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2003	1997		
Units: Patients	3	5		

Statistical analyses

Statistical analysis title	Secondary endpoint: definite stent thrombosis
Comparison groups	Clopidogrel v Placebo
Number of subjects included in analysis	4000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	6.96

Secondary: Secondary: Myocardial infarction

End point title	Secondary: Myocardial infarction

End point description:

End point type	Secondary

End point timeframe:
at 9 months after randomization, i.e. 15 months after the index intervention

End point values	Clopidogrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2003	1997		
Units: Patients	14	13		

Statistical analyses

Statistical analysis title	Secondary endpoint: myocardial infarction
Comparison groups	Clopidogrel v Placebo
Number of subjects included in analysis	4000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.97

Secondary: Secondary: Stroke	
End point title	Secondary: Stroke
End point description:	
End point type	Secondary
End point timeframe:	
at 9 months after randomization, i.e. 15 months after the index intervention	

End point values	Clopidogrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2003	1997		
Units: Patients	5	7		

Statistical analyses

Statistical analysis title	Secondary endpoint: stroke
Comparison groups	Clopidogrel v Placebo
Number of subjects included in analysis	4000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	4.41

Secondary: Secondary: TIMI major bleeding

End point title	Secondary: TIMI major bleeding

End point description:

End point type	Secondary

End point timeframe:

at 9 months after randomization, i.e. 15 months after the index intervention

End point values	Clopidogrel	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2003	1997		
Units: Patients	5	4		

Statistical analyses

Statistical analysis title	Secondary endpoint: TIMI major bleeding
Comparison groups	Clopidogrel v Placebo
Number of subjects included in analysis	4000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	2.98

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

ddIn case of a Serious Adverse Event (SAE) it is the responsibility of the local principal investigator (PI) to ensure that the AEF will be faxed to the ISAResearch Center within 24 hours of knowledge of the event. Reporting of not serious AEs within 3 m.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Clopidogrel 75 mg

Reporting group description:

A detailed analysis of non-serious adverse events was not performed, so "0" was entered for "Subjects affected by non-serious adverse events".

Reporting group title	Placebo

Reporting group description:

A detailed analysis of non-serious adverse events was not performed, so "0" was entered for "Subjects affected by non-serious adverse events".

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: A detailed analysis of non-serious adverse events was not performed.

Serious adverse events	Clopidogrel 75 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	315 / 2003 (15.73%)	300 / 1997 (15.02%)	
number of deaths (all causes)	12	8	
number of deaths resulting from adverse events	12	8	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibroma			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	4 / 2003 (0.20%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of ampulla of Vater			
subjects affected / exposed	0 / 2003 (0.00%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bladder cancer			
subjects affected / exposed	4 / 2003 (0.20%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 2003 (0.00%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	0 / 2003 (0.00%)	7 / 1997 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Carcinoma in situ of larynx			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric adenoma			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Larynx carcinoma			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lip squamous cell carcinoma			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoma			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver carcinoma			

subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver tumor			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of floor of mouth			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melanoma			
subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic cancer			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Porocarcinoma			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate adenoma			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal cancer			

subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal carcinoma			
subjects affected / exposed	3 / 2003 (0.15%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Schwannoma benign			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin tumor			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinocellular carcinoma			
subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urothelial carcinoma (bleeding)			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urothelial carcinoma			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
AION			
subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aneurysm cerebral			

subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	2 / 2003 (0.10%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bleeding			
subjects affected / exposed	37 / 2003 (1.85%)	13 / 1997 (0.65%)	
occurrences causally related to treatment / all	21 / 37	0 / 13	
deaths causally related to treatment / all	1 / 1	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral microangiopathy			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Claudication			
subjects affected / exposed	0 / 2003 (0.00%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery aneurysm			
subjects affected / exposed	1 / 2003 (0.05%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	12 / 2003 (0.60%)	7 / 1997 (0.35%)	
occurrences causally related to treatment / all	0 / 12	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischemic colitis			

subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leg ischemia			
subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial disease			
subjects affected / exposed	12 / 2003 (0.60%)	10 / 1997 (0.50%)	
occurrences causally related to treatment / all	0 / 12	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery stenosis			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			
subjects affected / exposed	6 / 2003 (0.30%)	7 / 1997 (0.35%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis venous deep			
subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcus cruris			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose veins			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous occlusion			

subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Amputation			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure excision			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker insertion			
subjects affected / exposed	3 / 2003 (0.15%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker replacement			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac resynchronisation therapy / implantable cardioverter defibrillator replacement			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystectomy			
subjects affected / exposed	0 / 2003 (0.00%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CRT/ICD insertion			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterostomy closure			

subjects affected / exposed	0 / 2003 (0.00%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facetectomy			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Finger operation			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart valve operation			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia repair			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip replacement			
subjects affected / exposed	7 / 2003 (0.35%)	4 / 1997 (0.20%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implantable defibrillator insertion			
subjects affected / exposed	4 / 2003 (0.20%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc operation			
subjects affected / exposed	2 / 2003 (0.10%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint prosthesis replacement			

subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee operation			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee prosthesis insertion			
subjects affected / exposed	4 / 2003 (0.20%)	4 / 1997 (0.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus operation			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microdiscectomy			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-target vessel revascularization			
subjects affected / exposed	18 / 2003 (0.90%)	19 / 1997 (0.95%)	
occurrences causally related to treatment / all	0 / 18	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polypectomy			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate surgery			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Removal of internal fixation			

subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal retransplantation			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shoulder operation			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovectomy			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Target vessel revascularization			
subjects affected / exposed	16 / 2003 (0.80%)	16 / 1997 (0.80%)	
occurrences causally related to treatment / all	0 / 16	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon operation			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toe amputation			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth extraction			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transurethral bladder resection			

subjects affected / exposed	1 / 2003 (0.05%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TURP			
subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine abrasion			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve replacement			
subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Swelling arm			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling of limbs			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	23 / 2003 (1.15%)	22 / 1997 (1.10%)	
occurrences causally related to treatment / all	0 / 23	0 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound healing disturbance			
subjects affected / exposed	2 / 2003 (0.10%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Allergic reaction			
subjects affected / exposed	1 / 2003 (0.05%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 2003 (0.05%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Hyperplasia of the prostate			
subjects affected / exposed	3 / 2003 (0.15%)	3 / 1997 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 2003 (0.10%)	6 / 1997 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic attack			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	18 / 2003 (0.90%)	18 / 1997 (0.90%)	
occurrences causally related to treatment / all	0 / 18	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	1 / 2003 (0.05%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vocal cord dysfunction			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord polyp			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Cardiac pacemaker malfunction			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Displaced lead cardiac pacemaker			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paravalvular leak			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Angiogram coronary			
subjects affected / exposed	3 / 2003 (0.15%)	8 / 1997 (0.40%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac stress test abnormal			
subjects affected / exposed	5 / 2003 (0.25%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatine kinase increased			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver biopsy			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shoulder arthroscopy			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress echocardiogram abnormal			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (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			
Accident			
subjects affected / exposed	3 / 2003 (0.15%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol intoxication			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ankle fracture			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Avulsion fracture			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 2003 (0.10%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flexor tendon rupture			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body in urogenital tract			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture of clavicle			
subjects affected / exposed	1 / 2003 (0.05%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture of vertebra			
subjects affected / exposed	1 / 2003 (0.05%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			

subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 2003 (0.05%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 2003 (0.05%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leg fracture			
subjects affected / exposed	1 / 2003 (0.05%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 2003 (0.00%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	14 / 2003 (0.70%)	13 / 1997 (0.65%)	
occurrences causally related to treatment / all	0 / 14	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	49 / 2003 (2.45%)	44 / 1997 (2.20%)	
occurrences causally related to treatment / all	0 / 49	0 / 44	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	2 / 2003 (0.10%)	12 / 1997 (0.60%)	
occurrences causally related to treatment / all	0 / 8	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 2003 (0.10%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (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	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Decompensation cardiac			
subjects affected / exposed	3 / 2003 (0.15%)	4 / 1997 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dressler's syndrome			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrasystoles			
subjects affected / exposed	1 / 2003 (0.05%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure			
subjects affected / exposed	4 / 2003 (0.20%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bundle branch block left			

subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular systolic dysfunction			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve insufficiency			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitation			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	3 / 2003 (0.15%)	3 / 1997 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 3	
Vasovagal reaction			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			

subjects affected / exposed	3 / 2003 (0.15%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 2003 (0.05%)	3 / 1997 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Abducens nerve disorder			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	6 / 2003 (0.30%)	5 / 1997 (0.25%)	
occurrences causally related to treatment / all	1 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epileptic seizure			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial nerve paresis			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	8 / 2003 (0.40%)	9 / 1997 (0.45%)	
occurrences causally related to treatment / all	0 / 8	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
TIA			
subjects affected / exposed	6 / 2003 (0.30%)	6 / 1997 (0.30%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 2003 (0.10%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal prolapse			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	0 / 2003 (0.00%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epigastric pain			
subjects affected / exposed	4 / 2003 (0.20%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 2003 (0.10%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 2003 (0.05%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 2003 (0.00%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar hernia			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstipation			
subjects affected / exposed	1 / 2003 (0.05%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal polyp			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver cholestasis			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute renal failure			
subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 2003 (0.05%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal insufficiency			
subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal stone			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			

subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Achilles tendon rupture			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankylosis of joint of shoulder region			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthrosis			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biceps tendon rupture			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chondropathy			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dupuytren's contracture			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facet joint arthropathy			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallux valgus			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herniated disc			
subjects affected / exposed	1 / 2003 (0.05%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbago			
subjects affected / exposed	2 / 2003 (0.10%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumboischialgia			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscal degeneration			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathologic fracture of vertebrae			

subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic floor muscle weakness			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriatic arthritis			
subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Quadriceps tendon rupture			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal canal stenosis			
subjects affected / exposed	3 / 2003 (0.15%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			

subjects affected / exposed	2 / 2003 (0.10%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis herpes			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fournier's gangrene			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection MRSA			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint infection			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			

subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlegmon			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 2003 (0.35%)	3 / 1997 (0.15%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory infection			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 2003 (0.10%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic arthritis			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary infection			
subjects affected / exposed	0 / 2003 (0.00%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 2003 (0.05%)	0 / 1997 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus exacerbated			

subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 2003 (0.00%)	2 / 1997 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalemia			
subjects affected / exposed	0 / 2003 (0.00%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			
subjects affected / exposed	2 / 2003 (0.10%)	1 / 1997 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Clopidogrel 75 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 2003 (0.00%)	0 / 1997 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2008	Substantial Amendment 14.11.2008: Protocol Amendment, PV 7.0 (29.10.2008) - Protocol Synopsis: Acronym "ISAR-SAFE" added - Wording of key exclusion criterion changed: "STEMI and Non-STEMI < 6 months after DES" - Text in Abstract/Background deleted: details to Kaiser-Permanent study and "Of note, in patients with acute myocardial infarction the continuation of dual antiplatelet therapy for more than 6 months seems to be beneficial . Therefore patients with acute myocardial infarction within the last six months will be excluded from this trial." - Exclusion criterion no. 5 specified: ST-elevation and non-ST-elevation (instead of "acute") myocardial infarction during the last 6 months after DES implantation - Specification randomization: patients meeting the eligibility criteria will be randomized in the order they qualify. Randomization will be performed between an additional 6 m period of clopidogrel or placebo with a randomization sequence of 1:1. New block size: 6 instead of 10 - Protocol section 6.6: details to unblinding (only in emergency case), emergency passport and hotline - Discontinuation of study drug: Added: "4. Implicit need for thienopyridine therapy, such as ticlid, clopidogrel or prasugrel (for example in case of stroke or new PCI or PTA during study period)." Study data will be analyzed according intention to treat principle - AE reporting (AE/SAE/SUSAR): reporting timelines and necessary documentation specified; after assessment by local Principal Investigator the sponsor performs evaluation with respect to seriousness, causality and expectedness of event - ECG Core Laboratory specified: a twelve lead ECG will be obtained prior to randomization according to the Study Schedule. These ECGs will be reviewed by the investigator and stored on site with the subject`s clinical study folder. The ECGs will serve as a comparison for repeat ECGs obtained in the event the subject develops clinical symptoms of ischemia - Appendices 1, 3, 5 updated

14 May 2009	Substantial Amendment 14.05.2009: Protocol Amendment, PV 8.1 (Apr 2009) - Period for the following inclusion criterion has been specified: patients on clopidogrel therapy at 6 months, the additional specification is „- 1/+2 months" - Changed wording of study objective: the objective of this study is to test the hypothesis that a clopidogrel therapy duration of 6 months after DES implantation is non-inferior to a 12 months therapy in terms of clinical outcomes (composite of death, myocardial infarction, stent thrombosis, stroke or major bleeding) - Primary endpoint „stent thrombosis" specified as „definite or propable" - Secondary endpoint "incidence of major bleeding" specified as "incidence of TIMI major bleeding" - The study design characterized the study population as patients on clopidogrel therapy at 6 months after DES implantation who do not require a reintervention. Condition "requirement of reintervention" deleted - Additional exclusion criterion no. 13: "prior enrolment in the same clinical trial" - Pre-enrolment procedures: some screening laboratory tests have been deleted, one has been added: C-reactive protein (CRP) - Specification of randomization: randomization will be stratified by center. Randomly permuted block lengths will be used - Concomitant therapy with aspirin changed from 100-200mg/day to 85-200mg/day - Unblinding must be performed only in cases when treating physician decides to give blood products to counteract the clopidogrel action (emergency operation; severe bleeding complications) - Description of analytical plan has been changed; text supplement: "The main analysis will be performed by testing for non-inferiority in terms of the incidence of the primary endpoint at 9 months after randomization. Test will be one-sided and an alpha level of 0.05 will be considered statistically significant." - Patients will not longer be identified by a CRF number, but by a patient ID and a randomization number - Appendices 1 and 3 updated
20 October 2010	Substantial Amendment 20.10.2010: Protocol Amendment, Protocol Version 9.0 (21.09.2010) - Pre-enrolment Procedures: screening laboratory tests are no longer carried out. - Randomization: allocation to treatment (computer generated sequence) is generated by the dispensary of the Deutsches Herzzentrum München. - Concomitant therapy: administration dose of aspirin has been changed from 85-200mg/day to 81-200mg/day. - Monitoring of trial safety: blinded interim analysis will be performed by the DSMB biostatistician if more than one-third and two-thirds of the planned number of patients has been enrolled (previous protocol version 8.1: if overall rate of these events is > 12% and > 1/3 of the planned number of patients have been enrolled). - Monitoring of trial safety: change of initial recommendation of early termination of the study by the DSMB; now it will be done if a difference with $P < 0.5$ is observed between the two study arms with respect to incidence of death, myocardial infarction, stent thrombosis, stroke or major bleeding (previous value: $P < 0.001$). - Monitoring and Audit: monitoring will be performed at 100% of Serious Adverse Events, as well as 100% of all data of randomly chosen 10% of all patients.
25 January 2011	Substantial Amendment 25.01.2011: Amendment of patient information (PIC V 6.0, 06.12.2010; Appendix of protocol version 9.0) Changes in Patient Information Form and Informed Consent Form: the documents have been revised in accordance with AMG.
23 November 2012	Substantial Amendment 23.11.2012, Protocol Amendment, Protocol Version 10.0 (29.10.2012) - Extension of study duration: the enrolment of a total of 6000 patients was not achieved in due time (31-Oct-2012); therefore the time window of the study has been extended (31-Dec-2014) - Change of Coordinating Principal Investigator: new Coordinating Principal Investigator is Prof. Dr. med. Adnan Kastrati, the former Coordinating Principal Investigator was Prof. Dr. med. Julinda Mehilli.

17 April 2014	Substantial Amendment 17.04.2014, Protocol Amendment, Protocol Version 10.2 (07.04.2014) Alteration of sample size: after performance of an interim analysis that showed a very low event rate the Data Safety Monitoring Board and the Steering Committee recommended not to exceed a sample size of 4000 patients (reduction from 6000 to 4000 patients).

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.

None reported

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25616646