

**Clinical trial results:****Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation catheter Ablation: Comparison to vitamin K antagonist therapy.****Summary**

EudraCT number	2014-002442-45
Trial protocol	DE BE DK GB NL ES AT
Global end of trial date	12 September 2017

Results information

Result version number	v1 (current)
This version publication date	27 May 2022
First version publication date	27 May 2022
Summary attachment (see zip file)	AXAFA-AFNET 5 Appendix 1 (2_AXAFA_CSR_Appendix 1_Tables_20180909.pdf) AXAFA-AFNET 5 Appendix 2 (3_AXAFA_CSR_Appendix 2_SAE_listing_death_narratives_20180909.pdf) AXAFA-AFNET 5 Report Synopsis (1_AXAFA_CSR_final_20180909_sig.pdf) AXAFA-AFNET 5 Appendix 3 (4_AXAFA_CSR_Appendix 3_Protocol Versions_20180909.pdf)

Trial information**Trial identification**

Sponsor protocol code	AXAFA_AFNET5
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Additional study identifiers

ISRCTN number	ISRCTN87711003
ClinicalTrials.gov id (NCT number)	NCT02227550
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Kompetenznetz Vorhofflimmern e.V. (AFNET) [Atrial Fibrillation NETwork]
Sponsor organisation address	Mendelstraße 11, Münster, Germany, 48149
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	
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
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 January 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that anticoagulation with the direct factor Xa inhibitor apixaban is not less safe than VKA therapy in patients undergoing catheter ablation of non-valvular AF in the prevention of peri-procedural complications.

Protection of trial subjects:

Procedural safety was paramount in the context of AXAFA, and all means for a safe procedure were taken. The study was conducted in experienced centres on the plateau phase of their learning curve. Pre-study assessment of all centres guaranteed sufficient experience in PVI procedures. Evaluation of experimental or novel ablation devices was not permitted in the AXAFA trial. The exact ablation technique should follow local routine and adhere to the recommendations of the AFNET/EHRA/ECAS consensus statement on catheter ablation of AF, and to the locally applicable AF guidelines. Local routine should guide details of the procedure (e.g. the type of ablation and mapping system used, or the choice of ablation energy) within the limits of these recommendations.

Background therapy:

All patients in AXAFA underwent catheter ablation of AF while on continued oral anticoagulation as described above. Silent brain lesions were assessed a sub-study by brain MRI 3-48 hours after the ablation procedure.

Evidence for comparator:

To demonstrate that anticoagulation with the direct factor Xa inhibitor apixaban is not less safe than VKA therapy in patients undergoing catheter ablation of non-valvular AF in the prevention of peri-procedural complications.

Patients randomised to the VKA group received oral anticoagulation using the locally used, marketed VKA, e.g. warfarin, phenprocoumon, acecoumarol, or fluindione. First intake of study medication was ensured at study enrolment (taking into consideration the change management instructions).

Actual start date of recruitment	27 February 2015
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	Netherlands: 109
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Austria: 33

Country: Number of subjects enrolled	Belgium: 135
Country: Number of subjects enrolled	Denmark: 138
Country: Number of subjects enrolled	Germany: 103
Country: Number of subjects enrolled	Italy: 67
Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	674
EEA total number of subjects	620

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)	357
From 65 to 84 years	317
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 27 February 2015 and ended on 10 April 2017 and was performed in Austria, Belgium, Germany, Denmark, Spain, Great Britain, Italy, Netherlands and the USA.

Pre-assignment

Screening details:

The intended population for this study is patients scheduled for catheter ablation of AF. Patients will be recruited by contracted study sites only, i.e. by approximately 50 sites performing catheter ablation for AF in clinical routine.

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	Xa Group

Arm description:

Patients randomised to the Xa group receive apixaban 5 mg twice daily throughout the study duration. Apixaban will be continued during the ablation procedure with twice daily dosing. The apixaban dose is reduced to 2.5 mg twice daily in patients who fulfil two of the following criteria at the time of randomisation: (chronic kidney disease or 60 kg body weight or less or age 80 years or more).

Arm type	Experimental
Investigational medicinal product name	Apixaban
Investigational medicinal product code	BMS-562247
Other name	Eliquis
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients randomised to the Xa group receive apixaban 5 mg twice daily throughout the study duration. Apixaban will be continued during the ablation procedure with twice daily dosing. The apixaban dose is reduced to 2.5 mg twice daily in patients who fulfil two of the following criteria at the time of randomisation: (chronic kidney disease or 60 kg body weight or less or age 80 years or more).

Arm title	VKA group
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Arm description:

Patients randomised to the VKA group will receive oral anticoagulation using the locally used, marketed VKA, e.g. warfarin, phenprocoumon, acecoumarol, or fluindione. First intake of study medication needs to be ensured at study enrolment (taking into consideration the change management instructions). VKAs will be prescribed as in clinical routine and dispensed by local hospital pharmacy. VKA therapy will be monitored by INR measurements according to applicable medical guidelines and to local routine policy.

Arm type	Active comparator
Investigational medicinal product name	Vitamin K Antagonist
Investigational medicinal product code	
Other name	Warfarin, Phenprocoumon, Acecoumarol, Fluindione
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients randomised to the VKA group will receive oral anticoagulation using the locally used, marketed VKA, e.g. warfarin, phenprocoumon, acecoumarol, or fluindione. First intake of study medication needs to be ensured at study enrolment. VKA therapy will be monitored by INR measurements according to applicable medical guidelines and to local routine policy.

Number of subjects in period 1	Xa Group	VKA group
Started	338	336
Completed	311	308
Not completed	27	28
Adverse event, serious fatal	5	5
Consent withdrawn by subject	16	19
Lost to follow-up	2	-
not specified	4	4

Baseline characteristics

Reporting groups

Reporting group title	overall trial
Reporting group description: -	

Reporting group values	overall trial	Total	
Number of subjects	674	674	
Age categorical			
mITT population			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	357	357	
From 65-84 years	317	317	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	221	221	
Male	453	453	

Subject analysis sets

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT Population: patients who started study drug and had the index catheter ablation procedure performed

Reporting group values	mITT		
Number of subjects	633		
Age categorical			
mITT population			
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)	337		
From 65-84 years	296		

85 years and over	0		
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Gender categorical Units: Subjects			
Female	209		
Male	424		

End points

End points reporting groups

Reporting group title	Xa Group
Reporting group description: Patients randomised to the Xa group receive apixaban 5 mg twice daily throughout the study duration. Apixaban will be continued during the ablation procedure with twice daily dosing. The apixaban dose is reduced to 2.5 mg twice daily in patients who fulfil two of the following criteria at the time of randomisation: (chronic kidney disease or 60 kg body weight or less or age 80 years or more).	
Reporting group title	VKA group
Reporting group description: Patients randomised to the VKA group will receive oral anticoagulation using the locally used, marketed VKA, e.g. warfarin, phenprocoumon, acecoumarol, or fluindione. First intake of study medication needs to be ensured at study enrolment (taking into consideration the change management instructions). VKAs will be prescribed as in clinical routine and dispensed by local hospital pharmacy. VKA therapy will be monitored by INR measurements according to applicable medical guidelines and to local routine policy.	
Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: mITT Population: patients who started study drug and had the index catheter ablation procedure performed	

Primary: Patients with primary endpoint: composite of all-cause death, stroke or major-bleeding

End point title	Patients with primary endpoint: composite of all-cause death, stroke or major-bleeding
End point description:	
End point type	Primary
End point timeframe:	
Overall trial	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: Number of subjects	22	23		

Statistical analyses

Statistical analysis title	Composite endpoint
Comparison groups	VKA group v Xa Group
Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0002
Method	Farrington and Manning non-inferiority

Primary: Death

End point title	Death ^[1]
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End point description:

End point type	Primary
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End point timeframe:

Overall trial

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis data provided for composite endpoint

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: Number of endpoint	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: Stroke or TIA

End point title	Stroke or TIA ^[2]
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End point description:

End point type	Primary
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End point timeframe:

Overall trial

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis data provided for composite endpoint

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: Number of endpoints	2	0		

Statistical analyses

No statistical analyses for this end point

Primary: Major Bleeding (BARC 2-5)

End point title	Major Bleeding (BARC 2-5) ^[3]
End point description:	
End point type	Primary
End point timeframe:	
Over all trial	
Notes:	
[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: Statistical analysis data provided for composite endpoint	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: Number of outcomes	20	25		

Statistical analyses

No statistical analyses for this end point

Primary: Bleeding requiring medical attention (BARC2)

End point title	Bleeding requiring medical attention (BARC2) ^[4]
End point description:	
End point type	Primary
End point timeframe:	
Over all trial	
Notes:	
[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: Statistical analysis data provided for composite endpoint	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: Number of endpoints	12	12		

Statistical analyses

No statistical analyses for this end point

Primary: Bleeding with haemoglobin drop of 30 to < 50 g/L or requiring transfusion (BARC 3a)

End point title	Bleeding with haemoglobin drop of 30 to < 50 g/L or requiring transfusion (BARC 3a) ^[5]
End point description:	

End point type	Primary
End point timeframe:	
Overall trial	
Notes:	
[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: Statistical analysis data provided for composite endpoint	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: Number of endpoints	5	4		

Statistical analyses

No statistical analyses for this end point

Primary: Bleeding with haemoglobin drop ≥ 50 g/L, or requiring surgery or iv vasoactive agents , or cardiac tamponade (BARC 3b)

End point title	Bleeding with haemoglobin drop ≥ 50 g/L, or requiring surgery or iv vasoactive agents , or cardiac tamponade (BARC 3b) ^[6]
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End point description:

End point type	Primary
End point timeframe:	
Over all trial	
Notes:	
[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: Statistical analysis data provided for composite endpoint	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: Number of endpoints	3	8		

Statistical analyses

No statistical analyses for this end point

Primary: Intracranial haemorrhage (BARC 3c)

End point title	Intracranial haemorrhage (BARC 3c) ^[7]
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End point description:

End point type	Primary
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End point timeframe:

Overall trial

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis data provided for composite endpoint

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	318		
Units: Number of endpoints	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: TIMI major bleeding (Intracranial bleed, or bleeding resulting in a haemoglobin drop of ≥ 50 g/L, or bleeding resulting in death within 7 days)

End point title	TIMI major bleeding (Intracranial bleed, or bleeding resulting in a haemoglobin drop of ≥ 50 g/L, or bleeding resulting in death within 7 days) ^[8]
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End point description:

End point type	Primary
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End point timeframe:

overall trial

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis data provided for composite endpoint

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: Number of endpoints	1	3		

Statistical analyses

No statistical analyses for this end point

Primary: ISTH major bleeding

End point title	ISTH major bleeding ^[9]
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End point description:

End point type	Primary
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End point timeframe:

Overall trial

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis data provided for composite endpoint

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: Number of endpoints	10	14		

Statistical analyses

No statistical analyses for this end point

Primary: Tamponade (Clinical type of bleeding event)

End point title	Tamponade (Clinical type of bleeding event) ^[10]
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End point description:

End point type	Primary
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End point timeframe:

Over all trial

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis data provided for composite endpoint

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: Number of endpoints	2	5		

Statistical analyses

No statistical analyses for this end point

Primary: Acces site bleed (Clinical type of bleeding event)

End point title	Acces site bleed (Clinical type of bleeding event) ^[11]
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End point description:

End point type	Primary
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End point timeframe:

Overall trial

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis data provided for composite endpoint

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: Number of endpoints	12	15		

Statistical analyses

No statistical analyses for this end point

Primary: Bleeding requiring transfusion of red blood cells (clinical type of bleeding event)

End point title	Bleeding requiring transfusion of red blood cells (clinical type of bleeding event) ^[12]
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End point description:

End point type	Primary
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End point timeframe:
overall trial

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis data provided for composite endpoint

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: Number of endpoints	2	1		

Statistical analyses

No statistical analyses for this end point

Primary: Other major bleed (Clinical type of bleeding event)

End point title	Other major bleed (Clinical type of bleeding event) ^[13]
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End point description:

End point type	Primary
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End point timeframe:
Overall trial

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis data provided for composite endpoint

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: NUmber of Endpoints	5	2		

Statistical analyses

No statistical analyses for this end point

Secondary: time from randomization to ablation days, median (q1, q3)

End point title	time from randomization to ablation days, median (q1, q3)
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End point description:

End point type	Secondary
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End point timeframe:

overall trial

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: days				
median (inter-quartile range (Q1-Q3))	34.0 (18.0 to 48.0)	36 (21 to 52.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Nights spent in hiospital after index ablation, median (q1, q3)

End point title	Nights spent in hiospital after index ablation, median (q1, q3)
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End point description:

End point type	Secondary
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End point timeframe:

overall trial

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: Nights				
median (inter-quartile range (Q1-Q3))	2 (1 to 5)	3 (2 to 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: ACT during ablation, seconds, median (q1, q3)

End point title	ACT during ablation, seconds, median (q1, q3)
End point description:	
End point type	Secondary
End point timeframe:	
overall trial	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: seconds				
median (inter-quartile range (Q1-Q3))	310.0 (273.0 to 350.0)	348.5 (304.0 to 396.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with at least one ACT value <250(n)

End point title	Number of subjects with at least one ACT value <250(n)
End point description:	
End point type	Secondary
End point timeframe:	
overall trial	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	315		
Units: Number of subjects	130	84		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with all ACT values in range (n)

End point title	Number of subjects with all ACT values in range (n)
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End point description:

End point type	Secondary
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End point timeframe:

overall trial

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	315		
Units: Number of subjects	73	161		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with at least one ACT value <300(n)

End point title	Number of subjects with at least one ACT value <300(n)
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End point description:

End point type	Secondary
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End point timeframe:

overall trial

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	315		
Units: Number of subjects	243	154		

Statistical analyses

No statistical analyses for this end point

Secondary: number of bleeding events (n)

End point title	number of bleeding events (n)
End point description:	
End point type	Secondary
End point timeframe:	
overall trial	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	315		
Units: number of events	54	64		

Statistical analyses

No statistical analyses for this end point

Secondary: Patients without recurrence of atrial fibrillation (n)

End point title	Patients without recurrence of atrial fibrillation (n)
End point description:	
End point type	Secondary
End point timeframe:	
overall trial	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	311	308		
Units: number of patients	217	217		

Statistical analyses

No statistical analyses for this end point

Secondary: SF-12 physical components score at end of study, median (q1, q3)

End point title	SF-12 physical components score at end of study, median (q1, q3)
End point description:	
End point type	Secondary
End point timeframe: overall trial	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	275		
Units: SF-12 score				
median (inter-quartile range (Q1-Q3))	48.4 (41.9 to 54.2)	48.8 (42.2 to 54.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-12 physical component score at end of study compared to baseline (d PCS), median (q1, q3)

End point title	Change in SF-12 physical component score at end of study compared to baseline (d PCS), median (q1, q3)
End point description:	
End point type	Secondary
End point timeframe: overall trial	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280	267		
Units: change in score				
median (inter-quartile range (Q1-Q3))	2.4 (-2.2 to 7.9)	2.8 (-2.0 to 8.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: SF-12 mental component score at end of study, median (q1, q3)

End point title	SF-12 mental component score at end of study, median (q1, q3)
End point description:	
End point type	Secondary
End point timeframe:	
overall trial	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	290	267		
Units: SF-12 mental componen t score				
median (inter-quartile range (Q1-Q3))	54.2 (45.8 to 58.3)	54.5 (46.6 to 59.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-12 mental component score at end of study compared to baseline (d MCS) n(%), median (q1, q3)

End point title	Change in SF-12 mental component score at end of study compared to baseline (d MCS) n(%), median (q1, q3)
End point description:	
End point type	Secondary
End point timeframe:	
overall trial	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	267		
Units: Change in SF-12 score				
median (inter-quartile range (Q1-Q3))	0.4 (-3.6 to 8.0)	1.6 (-2.8 to 8.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Karnofsky score at end of study, median (q1, q3)

End point title	Karnofsky score at end of study, median (q1, q3)
End point description:	
End point type	Secondary
End point timeframe:	
overall trial	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	311	308		
Units: Karnofsky score				
median (inter-quartile range (Q1-Q3))	100 (90 to 100)	100 (90 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Karnofsky score at end of study compared to baseline (dKarnofsky), median (q1, q3)

End point title	Change in Karnofsky score at end of study compared to baseline (dKarnofsky), median (q1, q3)
End point description:	
End point type	Secondary
End point timeframe:	
overall trial	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	311	308		
Units: Change in Karnofsky score				
median (inter-quartile range (Q1-Q3))	10 (0 to 10)	10 (0 to 10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cognitive function at end of study (MoCA), median (q1, q3)

End point title	Cognitive function at end of study (MoCA), median (q1, q3)
End point description:	
End point type	Secondary
End point timeframe:	
overall trial	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305	302		
Units: MoCA score				
median (inter-quartile range (Q1-Q3))	28.0 (26.0 to 29.0)	28.0 (26.0 to 29.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Abnormal MoCA at baseline (<26), n

End point title	Abnormal MoCA at baseline (<26), n
End point description:	
End point type	Secondary
End point timeframe:	
Overall time	

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305	302		
Units: Subjects	75	66		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in MoCA at end of study compared to baseline, median (q1, q3)

End point title	Change in MoCA at end of study compared to baseline, median (q1, q3)
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End point description:

End point type	Secondary
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End point timeframe:
overall trial

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	296		
Units: change in MoCA				
median (inter-quartile range (Q1-Q3))	0.0 (-1.0 to 2.0)	1.0 (-1.0 to 2.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in patients with abnormal MoCA at end of study compared to baseline, n (%)

End point title	Change in patients with abnormal MoCA at end of study compared to baseline, n (%)
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End point description:

End point type	Secondary
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End point timeframe:
overall trial

End point values	Xa Group	VKA group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	305	302		
Units: change in MoCA score				
number (not applicable)	-5.1	-9.2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

30.03.2015 - 18.08.2017

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Vitamin K Antagonist
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Reporting group description:

All randomized patients who received VKA

Reporting group title	Apixaban
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Reporting group description:

All randomized patients who started Apixaban

Serious adverse events	Vitamin K Antagonist	Apixaban	
Total subjects affected by serious adverse events			
subjects affected / exposed	93 / 327 (28.44%)	88 / 328 (26.83%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haemorrhage			

subjects affected / exposed	2 / 327 (0.61%)	4 / 328 (1.22%)	
occurrences causally related to treatment / all	2 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	2 / 327 (0.61%)	3 / 328 (0.91%)	
occurrences causally related to treatment / all	2 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula			
subjects affected / exposed	2 / 327 (0.61%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 327 (0.31%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aneurysm			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cardioversion			
subjects affected / exposed	10 / 327 (3.06%)	11 / 328 (3.35%)	
occurrences causally related to treatment / all	0 / 12	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ablation			
subjects affected / exposed	5 / 327 (1.53%)	3 / 328 (0.91%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker insertion			

subjects affected / exposed	2 / 327 (0.61%)	3 / 328 (0.91%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Percutaneous coronary intervention			
subjects affected / exposed	2 / 327 (0.61%)	2 / 328 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion			
subjects affected / exposed	2 / 327 (0.61%)	2 / 328 (0.61%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot amputation			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia repair			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastectomy			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device implantation			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft			

subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast operation			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (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			
Catheter site haemorrhage			
subjects affected / exposed	15 / 327 (4.59%)	11 / 328 (3.35%)	
occurrences causally related to treatment / all	8 / 17	8 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	4 / 327 (1.22%)	4 / 328 (1.22%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 327 (0.31%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Pyrexia			
subjects affected / exposed	2 / 327 (0.61%)	3 / 328 (0.91%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 327 (0.31%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensation of foreign body			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			

subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
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			
Dyspnoea			
subjects affected / exposed	0 / 327 (0.00%)	2 / 328 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Coagulation time abnormal			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram change			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Troponin			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Vascular pseudoaneurysm			
subjects affected / exposed	10 / 327 (3.06%)	6 / 328 (1.83%)	
occurrences causally related to treatment / all	5 / 12	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burn oesophageal			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (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	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	31 / 327 (9.48%)	21 / 328 (6.40%)	
occurrences causally related to treatment / all	0 / 40	0 / 24	
deaths causally related to treatment / all	1 / 1	0 / 1	
Cardiac failure			
subjects affected / exposed	2 / 327 (0.61%)	8 / 328 (2.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pericarditis			
subjects affected / exposed	2 / 327 (0.61%)	7 / 328 (2.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial haemorrhage			
subjects affected / exposed	5 / 327 (1.53%)	2 / 328 (0.61%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 327 (0.61%)	4 / 328 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	3 / 327 (0.92%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 327 (0.31%)	2 / 328 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 327 (0.31%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			

subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular extrasystoles			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 327 (0.61%)	4 / 328 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 327 (0.31%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 327 (0.31%)	2 / 328 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	2 / 327 (0.61%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	2 / 327 (0.61%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phrenic nerve paralysis			
subjects affected / exposed	1 / 327 (0.31%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 327 (0.61%)	2 / 328 (0.61%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 327 (0.31%)	2 / 328 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (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	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb discomfort			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scleroderma			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (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			
Pneumonia			
subjects affected / exposed	8 / 327 (2.45%)	2 / 328 (0.61%)	
occurrences causally related to treatment / all	0 / 9	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 327 (0.61%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infection			
subjects affected / exposed	0 / 327 (0.00%)	2 / 328 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 327 (0.00%)	2 / 328 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
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 %

Non-serious adverse events	Vitamin K Antagonist	Apixaban	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 327 (10.40%)	44 / 328 (13.41%)	
Vascular disorders			
Groin hematoma			
subjects affected / exposed	11 / 327 (3.36%)	15 / 328 (4.57%)	
occurrences (all)	11	15	
Major bleed			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences (all)	0	1	
Bleeding varicose vein			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Electrical cardioversion			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Nonspecific chest pain			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences (all)	0	1	
Ankle edema			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences (all)	0	1	
Fatigue aggravated			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences (all)	0	1	
Fever			
subjects affected / exposed	3 / 327 (0.92%)	0 / 328 (0.00%)	
occurrences (all)	3	0	
Catheter site haemorrhage			
subjects affected / exposed	0 / 327 (0.00%)	2 / 328 (0.61%)	
occurrences (all)	0	2	
Immune system disorders			

Allergic reaction subjects affected / exposed occurrences (all)	0 / 327 (0.00%) 0	1 / 328 (0.30%) 1	
Respiratory, thoracic and mediastinal disorders Nasal mucus blood tinged subjects affected / exposed occurrences (all) Nose bleed subjects affected / exposed occurrences (all)	0 / 327 (0.00%) 0 3 / 327 (0.92%) 3	1 / 328 (0.30%) 1 2 / 328 (0.61%) 2	
Investigations Electrocardiogram ST segment elevation subjects affected / exposed occurrences (all) Echocardiogram abnormal subjects affected / exposed occurrences (all) Arterial catheterisation abnormal subjects affected / exposed occurrences (all) Oxygen saturation decreased subjects affected / exposed occurrences (all)	0 / 327 (0.00%) 0 0 / 327 (0.00%) 0 1 / 327 (0.31%) 1 0 / 327 (0.00%) 0	1 / 328 (0.30%) 1 1 / 328 (0.30%) 1 0 / 328 (0.00%) 0 1 / 328 (0.30%) 1	
Injury, poisoning and procedural complications Post procedural bleeding subjects affected / exposed occurrences (all) Eyelid haematoma subjects affected / exposed occurrences (all)	0 / 327 (0.00%) 0 1 / 327 (0.31%) 1	1 / 328 (0.30%) 1 0 / 328 (0.00%) 0	
Cardiac disorders Pericardial effusion subjects affected / exposed occurrences (all) Atrial tachycardia	0 / 327 (0.00%) 0	1 / 328 (0.30%) 1	

subjects affected / exposed occurrences (all)	1 / 327 (0.31%) 1	1 / 328 (0.30%) 1	
Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 327 (0.31%) 1	2 / 328 (0.61%) 2	
Palpitations subjects affected / exposed occurrences (all)	1 / 327 (0.31%) 1	0 / 328 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 327 (0.61%) 2	0 / 328 (0.00%) 0	
Phrenic nerve paralysis subjects affected / exposed occurrences (all)	0 / 327 (0.00%) 0	2 / 328 (0.61%) 2	
Migraine subjects affected / exposed occurrences (all)	0 / 327 (0.00%) 0	2 / 328 (0.61%) 2	
Syncope subjects affected / exposed occurrences (all)	1 / 327 (0.31%) 1	0 / 328 (0.00%) 0	
Eye disorders Eye haemorrhage subjects affected / exposed occurrences (all)	1 / 327 (0.31%) 1	0 / 328 (0.00%) 0	
Gastrointestinal disorders Anal bleeding subjects affected / exposed occurrences (all)	0 / 327 (0.00%) 0	1 / 328 (0.30%) 1	
Defaecation frequency increased subjects affected / exposed occurrences (all)	0 / 327 (0.00%) 0	1 / 328 (0.30%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	0 / 327 (0.00%) 0	2 / 328 (0.61%) 2	
Oesophageal discomfort			

subjects affected / exposed	1 / 327 (0.31%)	1 / 328 (0.30%)	
occurrences (all)	1	1	
Gastric disorder			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences (all)	1	0	
Gastric hypomotility			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences (all)	0	1	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences (all)	1	0	
Gingival bleeding			
subjects affected / exposed	1 / 327 (0.31%)	1 / 328 (0.30%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	0 / 327 (0.00%)	1 / 328 (0.30%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences (all)	1	0	
Tendon calcification			
subjects affected / exposed	1 / 327 (0.31%)	0 / 328 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2014	<ul style="list-style-type: none">• Patients can undergo catheter ablation within the trial after at least 30 days of continuous effective anticoagulation or earlier when atrial thrombi have been excluded by a clinically indicated TEE. It was added that a TEE performed within 6 hours prior to randomisation is considered valid.• A new appendix was added (Appendix VIII "List of strong inducers/inhibitors of P-gp and CYP3A4 which lead to contraindication for the combined use with apixaban") following a primary Ethics Committee's request.• A new exclusion criterion was added (E14 "Documented atrial thrombi less than 3 months prior to randomisation.") following a primary Ethics Committee's request.• Following a Competent Authority's request it was added that women of childbearing potential are required to perform a pregnancy test before first intake of the study medication. If clinical signs of pregnancy are present during intake of the study medication and up to an adequate interval after intake of study medication, a pregnancy test has to be performed.• In accordance with the SmPC of apixaban and following a Competent Authority's request it was added that liver function parameters have to be assessed prior to first intake of study medication.• More precise criteria for assessment of continuous effective anticoagulation in VKA patients prior to index catheter ablation (i.e. at least one INR value ≥ 2.0 prior to ablation and thereafter no value < 2.0 prior to ablation).• The list of conditions for which a patient is not to undergo MRI was extended following a primary Ethics Committee's request.
08 January 2015	<ul style="list-style-type: none">• Wording in section "Adverse Event Reporting" was adjusted following a Competent Authority's request.• Further it was specified that in addition to serious adverse events (SAEs), also "AEs of special interest" will be MedDRA coded.
20 February 2015	<ul style="list-style-type: none">• Following a Competent Authority's request correction of reporting period for SAEs in accordance with ENTR/CT-3 (2011/C 172/01).
21 July 2016	<p>Final valid US version:</p> <ul style="list-style-type: none">• The term "exploratory" in the context of primary outcome and secondary endpoints was deleted following a primary Ethics Committee's request.• Protocol sections "Sample Size and Power Calculation" and "Interim Analyses, Reassessment of the Sample Size" have been described more in detail following a primary Ethics Committee's enquiries.• Criteria for assessment of continuous effective anticoagulation in VKA patients prior to index catheter ablation was adapted: Because in clinical routine an INR value ≥ 2 directly prior to catheter ablation is often not achieved, the reduction of the minimum value of the last INR required prior to the index catheter ablation to ≥ 1.8 represents clinical practice better. Further requirement of documenting all INR measurements (minimum of three) was added to ensure continuous anticoagulation.• More concise description of the first intake of study medication was added in order to avoid misunderstandings.• Clarification according to the definition of SAEs and AEs judged as medically important events.• Modified Rankin Scale at baseline visit added and corresponding protocol appendix IX.• Specification with regard to procedure assessing for pericardial effusion after catheter ablation, i.e. instead of a transthoracic echocardiography (TTE) also an intracardiac echocardiography (ICE) can be performed.

02 November 2016	<p>Final EU version:</p> <ul style="list-style-type: none"> • The term “exploratory” in the context of primary outcome and secondary endpoints was deleted following a primary Ethics Committee’s request. • Protocol sections “Sample Size and Power Calculation” and “Interim Analyses, Reassessment of the Sample Size” have been described more in detail following a primary Ethics Committee’s enquiries. • Criteria for assessment of continuous effective anticoagulation in VKA patients prior to index catheter ablation was adapted: Because in clinical routine an INR value ≥ 2 directly prior to catheter ablation is often not achieved, the reduction of the minimum value of the last INR required prior to the index catheter ablation to ≥ 1.8 represents clinical practice better. Further requirement of documenting all INR measurements (minimum of three) was added to ensure continuous anticoagulation. • More concise description of the first intake of study medication was added in order to avoid misunderstandings. • Clarification according to the definition of SAEs and AEs judged as medically important events. • Modified Rankin Scale at baseline visit added and corresponding protocol appendix IX. • Specification with regard to procedure assessing for pericardial effusion after catheter ablation, i.e. instead of a transthoracic echocardiography (TTE) also an intracardiac echocardiography (ICE) can be performed. • Following a Competent Authority’s objection the wording in section “Adverse Event Reporting” has again been formulated as in the version of amendment 08.01.2015.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29579168>

<http://www.ncbi.nlm.nih.gov/pubmed/28130378>

<http://www.ncbi.nlm.nih.gov/pubmed/32142113>

<http://www.ncbi.nlm.nih.gov/pubmed/32725107>

<http://www.ncbi.nlm.nih.gov/pubmed/33046527>