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Study of peri-procedural anticoagulation in AF ablation

Safety and Efficacy of Uninterrupted Anticoagulation with Dabigatran Etexilate versus Warfarin in Patients Undergoing Catheter Ablation of Atrial Fibrillation: The RE-CIRCUIT™ Study

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On behalf of the RE-CIRCUIT™ Investigators

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Disclosures

- Lecture honoraria from Boehringer Ingelheim and Medtronic
- Consultant to Medtronic, Abbott Medical, and AtriCure

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Background

- Catheter ablation of atrial fibrillation (AF) is the most common ablation procedure performed today in major medical centers throughout the world
- Thromboembolic and bleeding events, including cardiac tamponade, are some of the most feared complications of AF ablation
- Prior studies have shown that performance of AF ablation on uninterrupted anticoagulation with a vitamin K antagonist (VKA) helps to minimize the risk of these complications, and is now a well established anticoagulation strategy at the time of AF ablation
- This approach is cumbersome as most AF patients are anticoagulated with a non-VKA oral anticoagulant (NOAC) prior to AF ablation. Therefore the VKA strategy requires transition to VKA therapy prior to ablation
- Dabigatran etexilate has established efficacy and safety for stroke prevention in patients with AF
- Data on the outcomes of AF ablation when performed on uninterrupted NOAC therapy are limited

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Objective and Study Design

- The objective of the RE-CIRCUIT study was to investigate the safety and efficacy of uninterrupted dabigatran versus warfarin for peri-procedural anticoagulation in patients undergoing catheter ablation of atrial fibrillation
- This prospective multicenter open-label clinical trial enrolled 704 patients across 104 sites in 11 countries between April 2015 and July 2016
- An independent blinded adjudication committee and data monitoring committee was incorporated in the study design.

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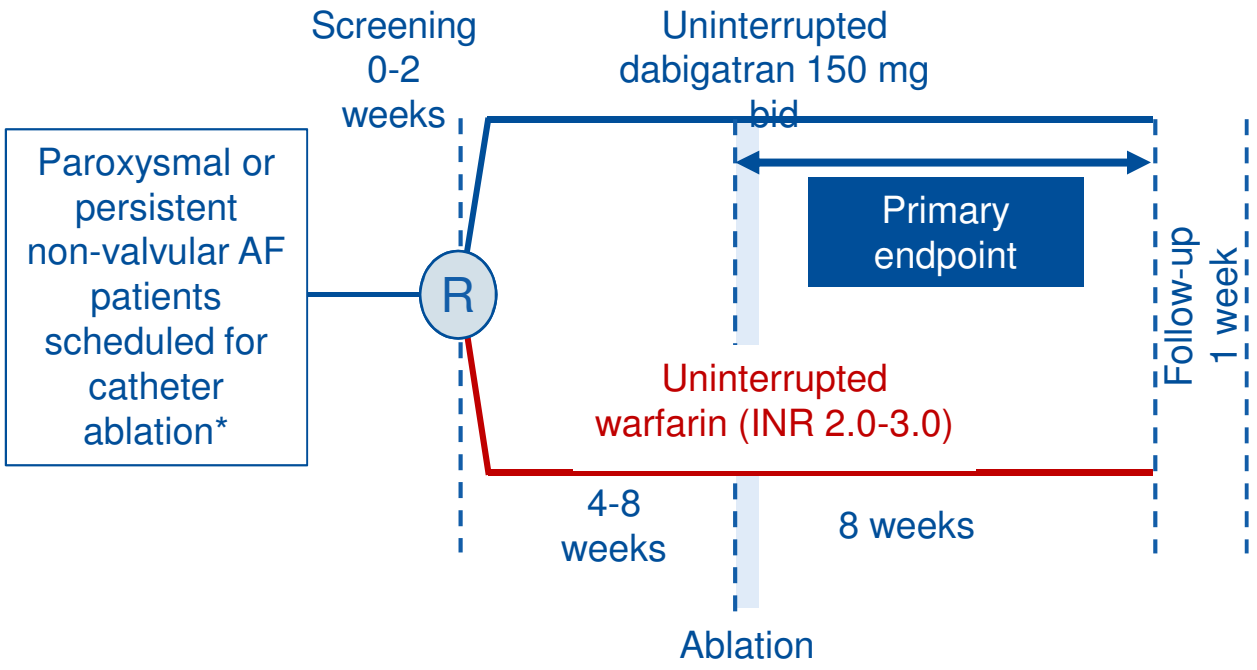
Study Design



- **Primary endpoint:** incidence of adjudicated ISTH MBEs during and up to 8 weeks post-ablation†
- **Secondary endpoints** included adjudicated thromboembolic events and bleeding events

*And eligible for dabigatran 150 mg bid according to local prescribing information.

†Primary end point assessed from the start of the ablation procedure and up to 8 weeks post-ablation

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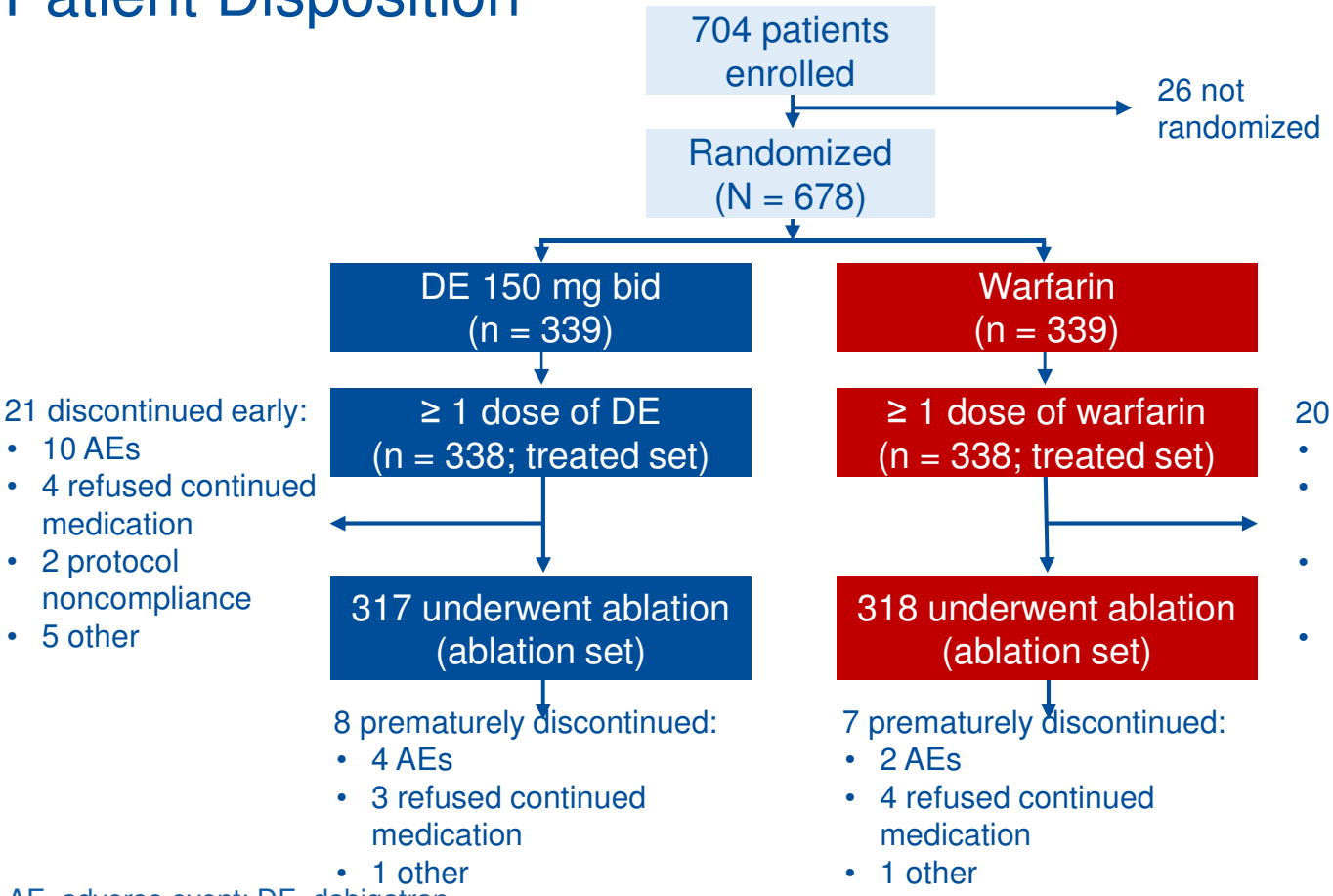
Patient Disposition



AE, adverse event; DE, dabigatran etexilate

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Baseline Demographics

Characteristics	Dabigatran 150 mg bid (n = 317)	Warfarin (n = 318)
Mean age (standard deviation), years	59.1 (10.4)	59.3 (10.3)
Atrial fibrillation, n (%)		
Paroxysmal	213 (67.2)	219 (68.9)
Persistent	86 (27.1)	81 (25.5)
Longstanding persistent	18 (5.7)	18 (5.7)
CHA_2DS_2-VASc score, mean	2.0	2.2
Medical history, n (%)		
Congestive heart failure	31 (9.8)	34 (10.7)
Hypertension	166 (52.4)	177 (55.7)
Diabetes mellitus	30 (9.5)	34 (10.7)
Previous stroke	10 (3.2)	9 (2.8)
Coronary artery disease	32 (10.1)	48 (15.1)
Previous myocardial infarction	10 (3.2)	15 (4.7)
Prior major bleeding or predisposition	3 (0.9)	4 (1.3)
TTR during study, mean %	66.4	

TTR time in therapeutic range of INR 2.0-3.0. *Based on treated set, n = 330.

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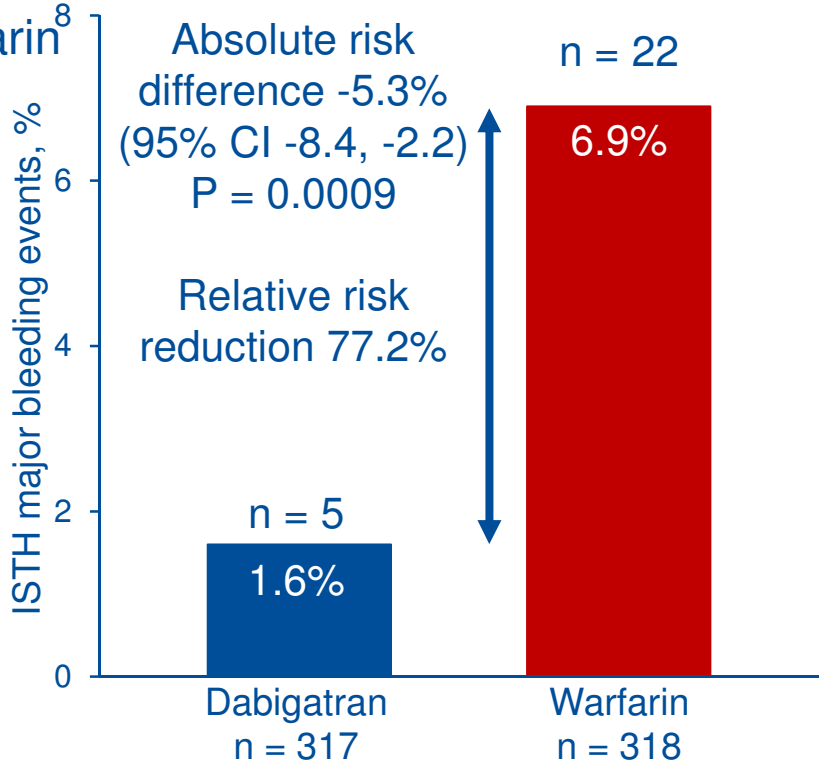
Results

- Patients on uninterupted dabigatran had significantly fewer MBEs as compared with patients on warfarin



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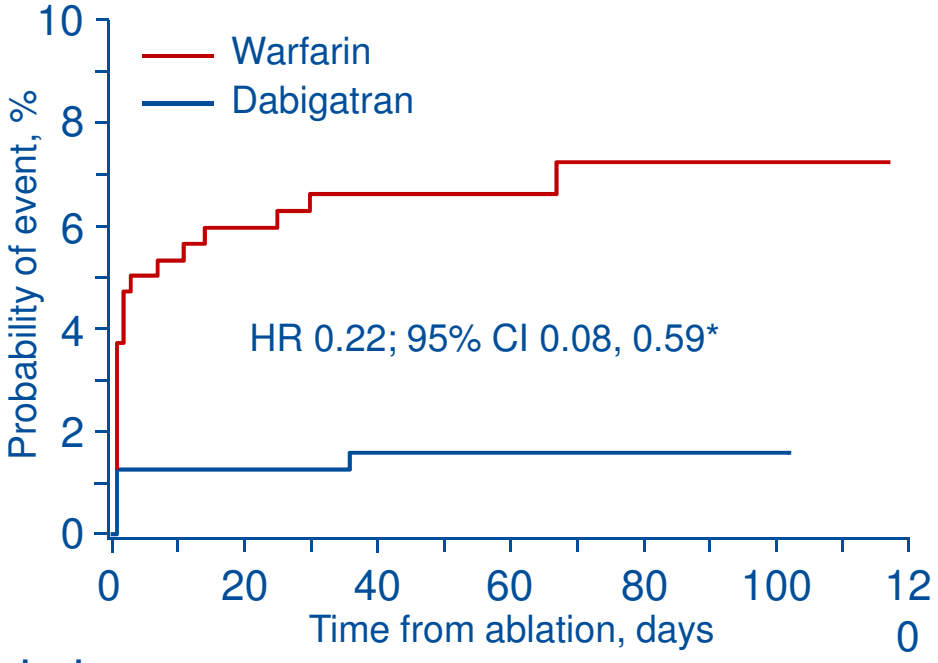
Fewer MBEs from the Time of Ablation



Patients at risk													
Dabigatran	317	313	311	311	306	305	297	83	4	2	1	0	0
Warfarin	318	301	297	296	295	295	278	85	13	5	3	1	0

*Cox proportional hazard model and Wald confidence limits.

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Sites and Management of ISTH MBEs

	Dabigatran	Warfarin
ISTH MBEs, n*	5	23†
Pericardial tamponade	1	6
Pericardial effusion	1	0
Groin bleed	2	2
Groin hematoma	0	8
Gastrointestinal bleed	1	2
Intracranial bleed	0	2
Pseudoaneurysm	0	1
Hematoma	0	2
Required medical action	4	21
Intervention/procedure	1	11

*Based on number of events rather than number of patients.
†One patient had two adjudicated ISTH MBEs.

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Results: Secondary Endpoints

Low Rate of Thromboembolic Events

- Stroke: no events
- Systemic embolism: no events
- Transient ischemic attack: dabigatran 0 vs warfarin 1

Minor Bleeding Events Similar Between Treatments

- Dabigatran 59 (18.6%) vs warfarin 54 (17.0%)

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Results

- Severe adverse events were less frequent for dabigatran
  - 11 (3.3%) vs 21 (6.2%) patients
- Adverse events leading to treatment discontinuation were more for dabigatran
  - 19 (5.6%) vs 8 (2.4%) patients
  - Mostly non-specific gastrointestinal adverse events for dabigatran
- Fewer events in the dabigatran group required hospitalization
  - 26 (7.7%) vs 34 (10.1%) patients
  - Or prolonged hospitalization 13 (3.8%) vs 22 (6.5%) patients
- No fatal events

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Summary

- Performance of AF ablation on uninterrupted dabigatran showed a significantly lower rate of major bleeding compared with warfarin
- Adjudicated major bleeds were reported in five dabigatran treated patients as compared with 22 warfarin-treated patients resulting in an absolute risk difference of –5.3% and a relative risk reduction of 77%
- There were no thrombotic events in patients receiving dabigatran and one event in the warfarin group
- No fatal events were reported with either treatment
- Rates of minor bleeding events were similar between treatments

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Conclusion

- In conclusion, the results of the RE-CIRCUIT study demonstrate that performance of AF ablation on uninterrupted dabigatran is a superior anticoagulation strategy
  as compared with performance of AF ablation on uninterrupted warfarin
- The availability of the reversal agent idarucizumab, while not needed in any patient in this trial, further motivates the adoption of uninterrupted dabigatran as an appropriate anticoagulation strategy in patients undergoing AF ablation

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Backup slides

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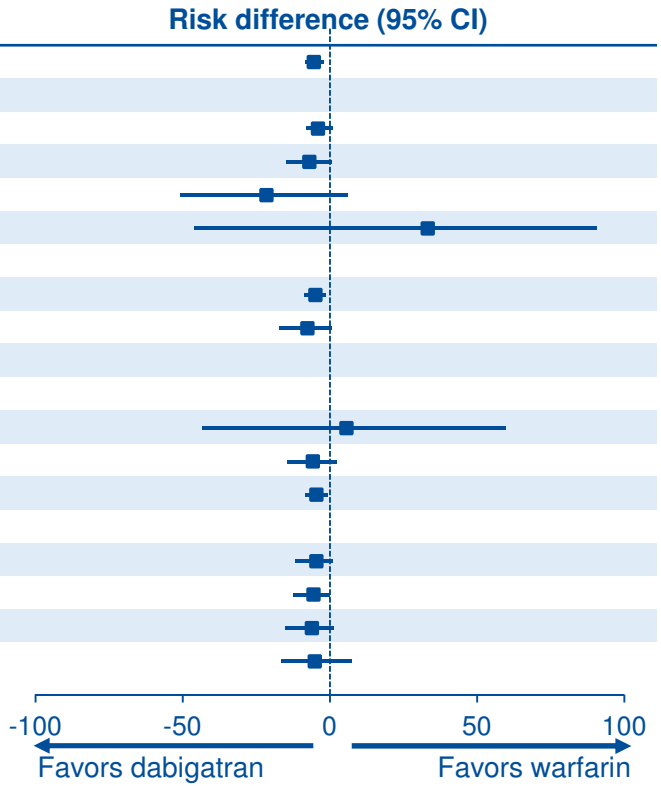
Subgroup Analysis of ISTH MBEs

	Dabigatran, n/N	Warfarin, n/N
Overall	5/317	22/318
Age, years		
<65	2/221	10/205
65 to <75	2/80	9/96
75 to <80	0/13	3/14
≥80	1/3	0/3
Gender		
Male	2/230	14/245
Female	3/87	8/73
Baseline creatinine clearance, ml/min		
<30*	0/0	0/0
30–50	1/5	1/7
50–80	1/64	5/69
≥80	3/235	13/227
Baseline BMI, kg/m²		
<25	1/92	5/89
25 to <30	2/118	8/111
30 to <35	1/71	5/67
≥35	1/36	4/51



*CI not calculated.

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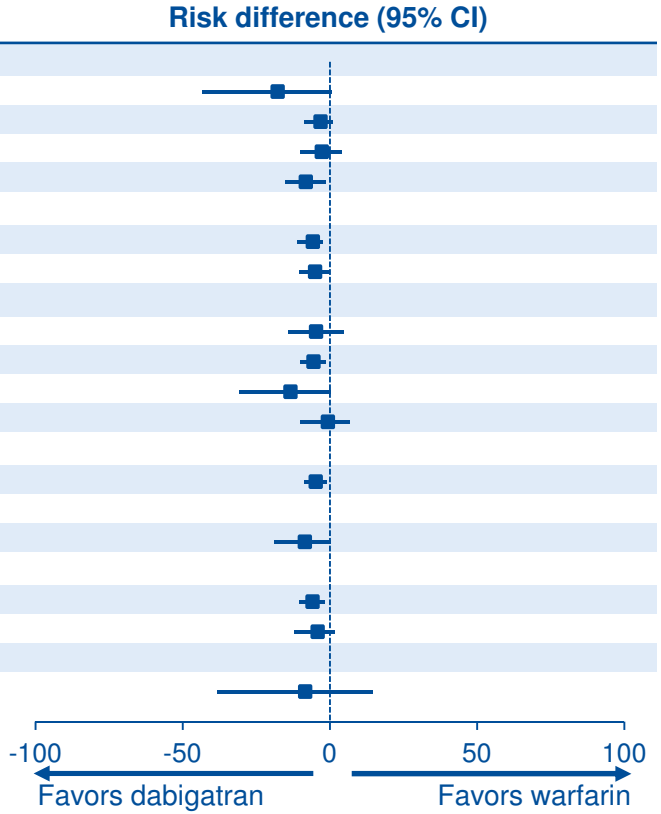
Subgroup Analysis of ISTH MBEs (Continued)

	Dabigatran, n/N	Warfarin, n/N
CHA_2DS_2-VASc score		
0	0/26	3/17
1	0/100	3/99
2	4/104	6/93
>2	1/87	10/109
Prior hypertension		
No	0/151	8/141
Yes	5/166	14/177
Region		
North America	3/65	7/76
Western Europe	1/163	10/166
Eastern Europe	0/27	4/30
Asia	1/62	1/46
Type of ablation		
PVI	4/244	16/251
Linear ablation*	0/1	0/0
Other techniques	1/64	6/60
Energy source of ablation		
Radiofrequency	4/206	17/220
Cryoballoon	1/86	4/76
Laserballoon*	0/0	0/1
Other energy sources	0/16	1/12



*CI not calculated.

PVI, pulmonary vein isolation.

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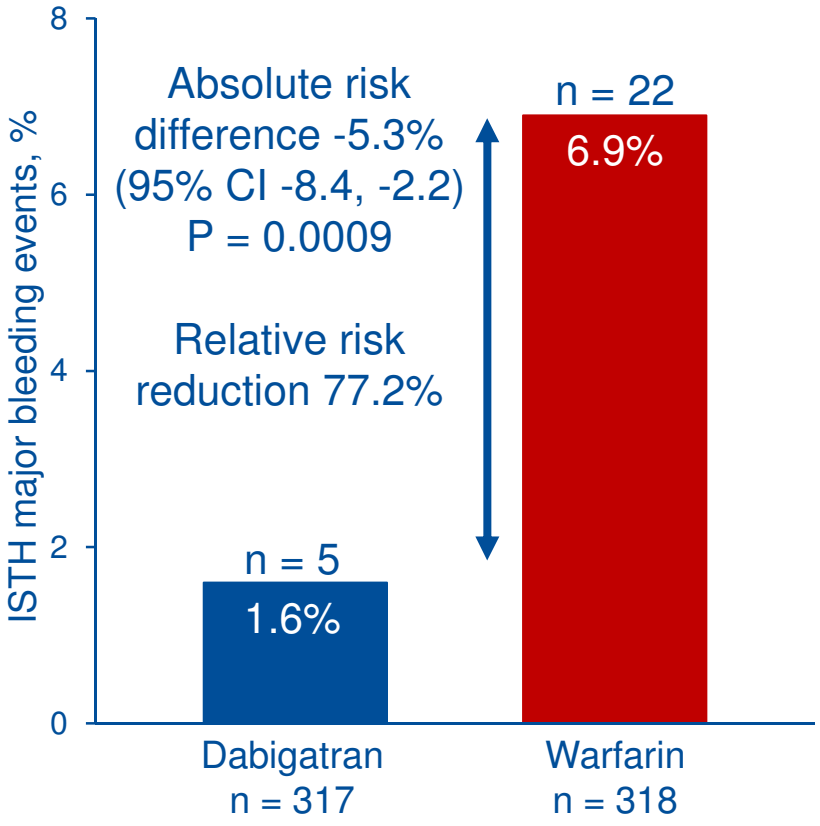
Baseline Demographics (Further Information)

Characteristics	Dabigatran 150 mg bid (n = 317)	Warfarin (n = 318)
Male, n (%)	230 (72.6)	245 (77.0)
Mean body mass index, kg/m^2	28.5	28.8
Other medical history, n (%)		
Left ventricular dysfunction	25 (7.9)	23 (7.2)
Percutaneous coronary intervention	16 (5.0)	19 (6.0)
Previous GI bleeding or gastritis	24 (7.6)	21 (6.6)
Renal diseases	7 (2.2)	14 (4.4)
Medication use, n (%)		
Vitamin K antagonists	95 (28.1)	86 (25.4)
Dabigatran	45 (13.3)	36 (10.7)
Rivaroxaban	29 (8.6)	29 (8.6)
Apixaban	21 (6.2)	30 (8.9)
Edoxaban	3 (0.9)	0 (0)
NSAIDs	66 (19.5)	78 (23.1)
Proton pump inhibitors	73 (21.6)	79 (23.4)
Statins	106 (31.4)	101 (29.9)
Beta-blockers	195 (57.7)	204 (60.4)

NSAID, non-steroidal anti-inflammatory drug.

INR Prior to and ACT During the Ablation



	Dabigatran	Warfarin
INR (mean) prior to ablation		
Patients with ISTH MBE	–	2.4
Patients without ISTH MBE	–	2.3
ACT mean, s		
Patients with ISTH MBE	374	314
Patients without ISTH MBE	329	344

ACT, activated clotting time

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Compliance with Dabigatran 150 mg bid

Characteristics	Dabigatran 150 mg bid
Compliance, %	230 (72.6)
Mean	97.6
Median	99.2
Medication taken, n (%)	99.2
50 to < 80 days	4 (1.3)
80 to < 120 days	312 (98.4)

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Frequency of Adverse Events Leading to Treatment Discontinuation

Characteristics	Dabigatran 150 mg bid (n = 317)	Warfarin (n = 318)
Gastritis erosive	0 (0.0)	1 (0.3)
Gastritis	2 (0.6)	0 (0.0)
Upper gastrointestinal hemorrhage	1 (0.3)	0 (0.0)
Abdominal pain upper	1 (0.3)	0 (0.0)
Atrial flutter	1 (0.3)	0 (0.0)
Lower respiratory tract infection	1 (0.3)	0 (0.0)
Hematoma	0 (0.0)	1 (0.3)
International normalized ratio fluctuation	0 (0.0)	1 (0.3)
Monoarthritis	0 (0.0)	1 (0.3)

Adjudicated ISTH MBEs Requiring Intervention

Study treatment	AE name (investigator assessment)	Days from* (related to)† ablation	Bleeding intervention/procedure reported†
Dabigatran	Cardiac tamponade	1 (Yes)	Drainage
Warfarin	Pericardial tamponade	1 (Yes)	Drainage
Warfarin	Pericardial tamponade	1 (Yes)	Drainage
Warfarin	Pericardial tamponade	1 (Yes)	Drainage
Warfarin	Pericardial tamponade	1 (Yes)	Drainage
Warfarin	Pericardial tamponade	1 (Yes)	Drainage
Warfarin	Hemopericardium	1 (Yes)	Pericardiocentesis
Warfarin	Pulsating hematoma	2 (Yes)	Suture closure of femoral arterial
Warfarin	Groin hematoma	2 (Yes)	Retroperitoneal intervention
Warfarin	Right groin hematoma	3 (Yes)	Surgical repair of right superficial femoral artery
Warfarin	Femoral artery pseudoaneurysm	14 (Yes)	Surgical repair of aneurysm
Warfarin	Gastrointestinal bleed	67 (No)	Polyps removed

n number of events rather than number of patients. One patient had two adjudicated ISTH MBEs.
*1 = day of ablation. †Investigator assessed.

Adjudicated ISTH MBEs Listings

Study treatment	Country	AE name (investigator assessment)	Days from ablation*	Related to ablation†	ACT mean, s	INR prior to ablation	Time in INR range 2–3, %	Bleeding medical action reported†
Dabigatran	USA	Pericardial effusion	1	Yes	317	–	–	Protamine
Dabigatran	J	Cardiac tamponade	1	Yes	397	–	–	Drainage, protamine
Dabigatran	UK	Vascular access major bleed	1	Yes	> 400‡	–	–	Protamine, bilateral femostop device
Dabigatran	USA	Groin bleed	1	No	274	–	–	No
Warfarin	CN	Hematoma at femoral puncture site	1	Yes	379	2.10	75	Protamine
Warfarin	CN	Pericardial tamponade	1	Yes	220	2.20	55	Drainage used, transfusion required, protamine, prothrombin complex concentrate
Warfarin	CN	Hematoma right groin	1	Yes	283	2.80	87	Protamine
Warfarin	CN	Right femoral hematoma	1	Yes	376	2.30	62	Prothrombin complex concentrate

Data based on number of events rather than number of patients. One patient had two adjudicated ISTH MBEs.
*1 = day of ablation. †Investigator assessed. ‡Only 2 values > 400 s reported. #No ACT values provided.
B, Belgium; CN, Canada; D, Germany; F, France; I, Italy; J, Japan; NL, Netherlands; RF, Russian Federation; UK, United Kingdom; USA, United States.

Adjudicated ISTH MBEs Listings (Continued)

Study treatment	Country	AE name (investigator assessment)	Days from ablation*	Related to ablation†	ACT mean, s	INR prior to ablation	Time in INR range 2–3, %	Bleeding medical action reported†
Warfarin	NL	Groin bleeding	1	Yes	401	2.80	69	SPICA cast
Warfarin	B	Exuding blood at surgical groin site	1	Yes	381	2.60	69	Yes, details not reported
Warfarin	F	Pericardial tamponade	1	Yes	334	3.40	32	Drainage, protamine
Warfarin	I	Inguinal hematoma	1	Yes	309	1.50	73	Yes, details not reported
Warfarin	I	Pericardial tamponade	1	Yes	220	2.41	25	Drainage, protamine
Warfarin	UK	Pericardial tamponade	1	Yes	359	2.20	60	Drainage
Warfarin	I	Inguinal hematoma	1	Yes	309	1.50	73	Yes, details not reported
Warfarin	DE	Pericardial tamponade	1	Yes	339	1.60	35	Drainage used, transfusion required, protamine, prothrombin complex concentrate

Data based on number of events rather than number of patients. One patient had two adjudicated ISTH MBEs.

*1 = day of ablation. †Investigator assessed. ‡Only 2 values > 400 s reported. #No ACT values provided.

B, Belgium; CN, Canada; DE, Germany; F, France; I, Italy; J, Japan; NL, Netherlands; RF, Russian Federation.

Adjudicated ISTH MBEs Listings (Continued)

Study treatment	Country	AE name (investigator assessment)	Days from ablation*	Related to ablation†	ACT mean, s	INR prior to ablation	Time in INR range 2–3, %	Bleeding medical action reported†
Warfarin	RF	Hemopericardium	1	Yes	286	2.20	74	Pericardiocentesis
Warfarin	RF	Pulsating hematoma	2	Yes	NR#	2.52	45	Suture closure of femoral arterial
Warfarin	J	Groin hematoma	2	Yes	323	2.45	67	Transfusion required, retroperitoneal intervention
Warfarin	DE	Hematoma right groin	2	Yes	286	3.50	51	No
Warfarin	F	Right groin hematoma	3	Yes	330	2.40	62	Transfusion required, surgical repair of the right superficial femoral artery
Warfarin	USA	Right groin hematoma	7	Yes	410	2.40	62	Yes, details not reported
Warfarin	I	Postoperative hematoma	11	Yes	212	2.51	22	Yes, details not reported
Warfarin	RF	Femoral artery pseudoaneurysm	14	Yes	278	1.95	48	Surgical repair of arteriotomy

Data based on number of events rather than number of patients. One patient had two adjudicated ISTH MBEs.

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Adjudicated ISTH MBEs Listings (Continued)

Study treatment	Country	AE name (investigator assessment)	Days from ablation*	Related to ablation†	ACT mean, s	INR prior to ablation	Time in INR range 2–3, %	Bleeding medical action reported†
Warfarin	USA	Gastric antral erosion	25	No	259	2.40	91	Transfusion required
Warfarin	RF	Intraventricular hemorrhage minimum volume	30	No	259	2.80	82	Yes, details not reported
Warfarin	RF	Soft tissue bruise neck	30	No	259	2.80	82	No
Dabigatran	CN	Upper gastrointestinal hemorrhage	36	No	508	–	–	Yes, details not reported
Warfarin	USA	Gastrointestinal bleed	67	No	352	2.32	63	Transfusion required, polyps removed

Data based on number of events rather than number of patients. One patient had two adjudicated ISTH MBEs.
*1 = day of ablation. †Investigator assessed. ‡Only 2 values > 400 s reported. #No ACT values provided.
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