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Clinical Benefit of Minimally-Interrupted Dabigatran versus Uninterrupted Warfarin for Catheter Ablation of Atrial Fibrillation: A Prospective Randomized Multicenter Trial

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for **ABRIDGE-J** (**AB**lation pe**RI**operative **D**abi**G**atran in use **E**nvisioning in **J**apan) Study Group.

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Background

Recent study (RE-CIRCUIT) has shown that dabigatran with no interruption is effective for reducing the risk of stroke at the time of ablation for nonvalvular atrial fibrillation, and has a lower bleeding risk than uninterrupted warfarin. However, the major bleeding events occurred in the patients who received the final dose of dabigatran less than 8 hours before ablation. Minimally-interrupted direct oral anticoagulants (DOAC) is currently widely used, while there are not enough controlled data.

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Objective and Study Design

OBJECTIVE: To compare the efficacy and safety of minimally-interrupted dabigatran as an anticoagulant therapy with that of uninterrupted warfarin in candidates for catheter ablation for non-valvular AF.

DESIGN: Randomized, open-label, multicenter, controlled trial with blinded adjudicated endpoint assessments with 12-month follow-up. Patients (n=500) were randomly assigned to receive either minimally-interrupted dabigatran (hold one to two doses prior the ablation) or uninterrupted warfarin.

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Study Design

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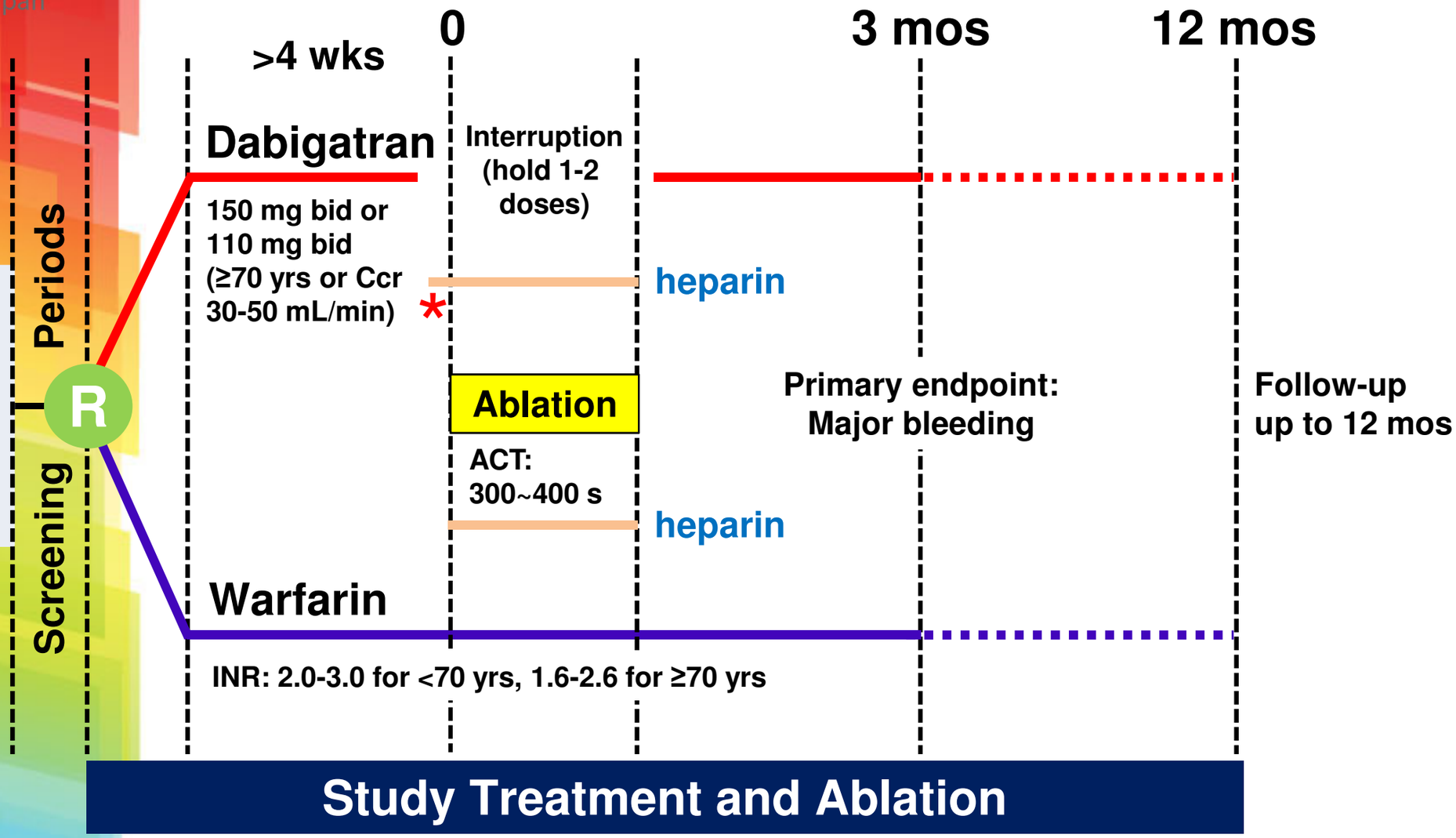
Patients aged 20-85 years with paroxysmal or persistent NVAF scheduled for initial catheter ablation



* If the interval between the final dose of D and the ablation (D-A interval) was ≥24 hours, heparin bridging was recommended.

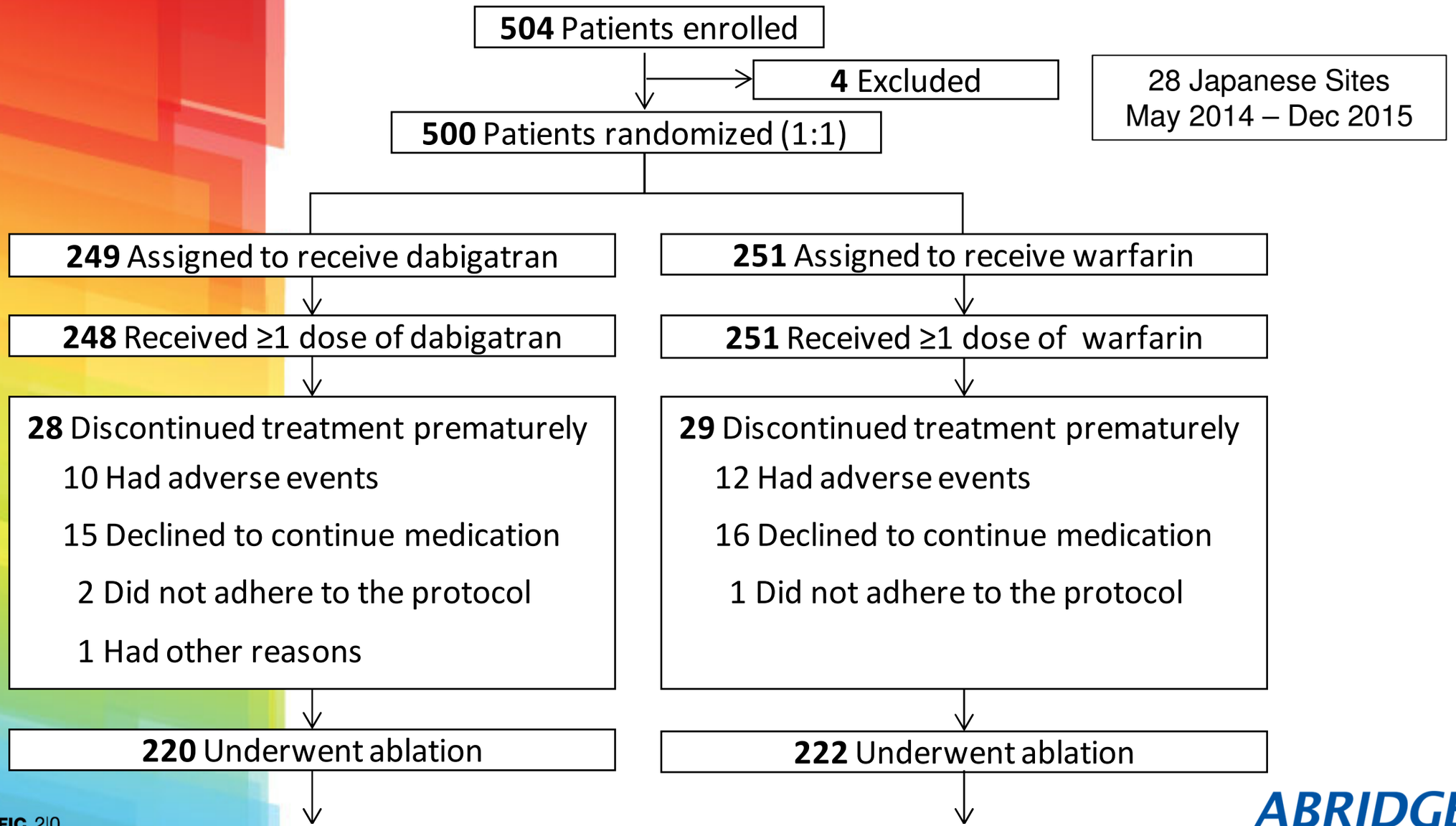
Endpoints

Primary endpoint: Incidence of adjudicated major bleeding events as defined by the ISTH during ablation procedure and up to 3 months after ablation.

Secondary endpoints: Composite of stroke, systemic embolism, or TIA; and all bleeding events; and a composite of major bleeding events and thromboembolic events.

All potential endpoint events reviewed by an independent events committee.

Enrollment, Randomization and Follow-up



Baseline Demographic and Clinical Characteristics

	Dabigatran (n=220)	Warfarin (n=222)
Age, years	63.8 ± 10.0	64.4 ± 9.8
Male gender, n	171 (77.7%)	160 (72.1%)
Body weight, Kg	67.39 ± 11.88	65.99 ± 11.25
BMI, Kg/m^2	24.45 ± 3.70	24.31 ± 3.56
CHA_2DS_2-VASc score	1.8 ± 1.4	1.9 ± 1.4
HAS-BLED score	1.3 ± 1.1	1.3 ± 1.0
Paroxysmal AF, n	138 (62.7%)	138 (62.2%)
Time from the first AF, years	3.1 ± 4.5	3.2 ± 4.0
Congestive heart failure, n	8 (3.6%)	14 (6.3%)
Diabetes mellitus, n	36 (16.4%)	34 (15.3%)
Hypertension, n	123 (55.9%)	126 (56.8%)
Previous stroke, n	15 (6.8%)	12 (5.4%)
Previous GI bleeding, n	0	3 (1.4%)
Aspirin, n	13 (5.9%)	14 (6.3%)
Clopidogrel, n	3 (1.4%)	3 (1.4%)
NSAIDs, n	1 (0.5%)	7 (3.2%)
LVEF, %	64.99 ± 8.42	64.46 ± 8.31
Creatinine clearance, mL/min	83.66 ± 27.46	82.05 ± 24.95
Systolic blood pressure, mmHg	130.2 ± 16.7	132.4 ± 18.1
Diastolic blood pressure, mmHg	78.4 ± 12.4	78.8 ± 11.9
Heart rate, bpm	73.4 ± 17.8	71.9 ± 17.3

Procedural Characteristics

	Dabigatran (n=220)	Warfarin (n=222)
Prior AF ablation, n	0	0
Trans-esophageal echo (TEE) within 48 hours, n	163 (74.1%)	154 (69.4%)
Intracardiac echo (ICE), n	52 (23.6%)	58 (26.1%)
TEE and/or ICE, n	188 (85.5%)	187 (84.2%)
RF PVI, n	176 (80.0%)	171 (77.0%)
Cryoballoon PVI, n	34 (15.5%)	44 (19.8%)
SVCI, n	40 (18.2%)	30 (13.5%)
RF CTI, n	124 (56.4%)	123 (55.4%)
Cryoablation CTI, n	25 (11.4%)	25 (11.3%)
Linear ablation, n	48 (21.8%)	47 (21.2%)

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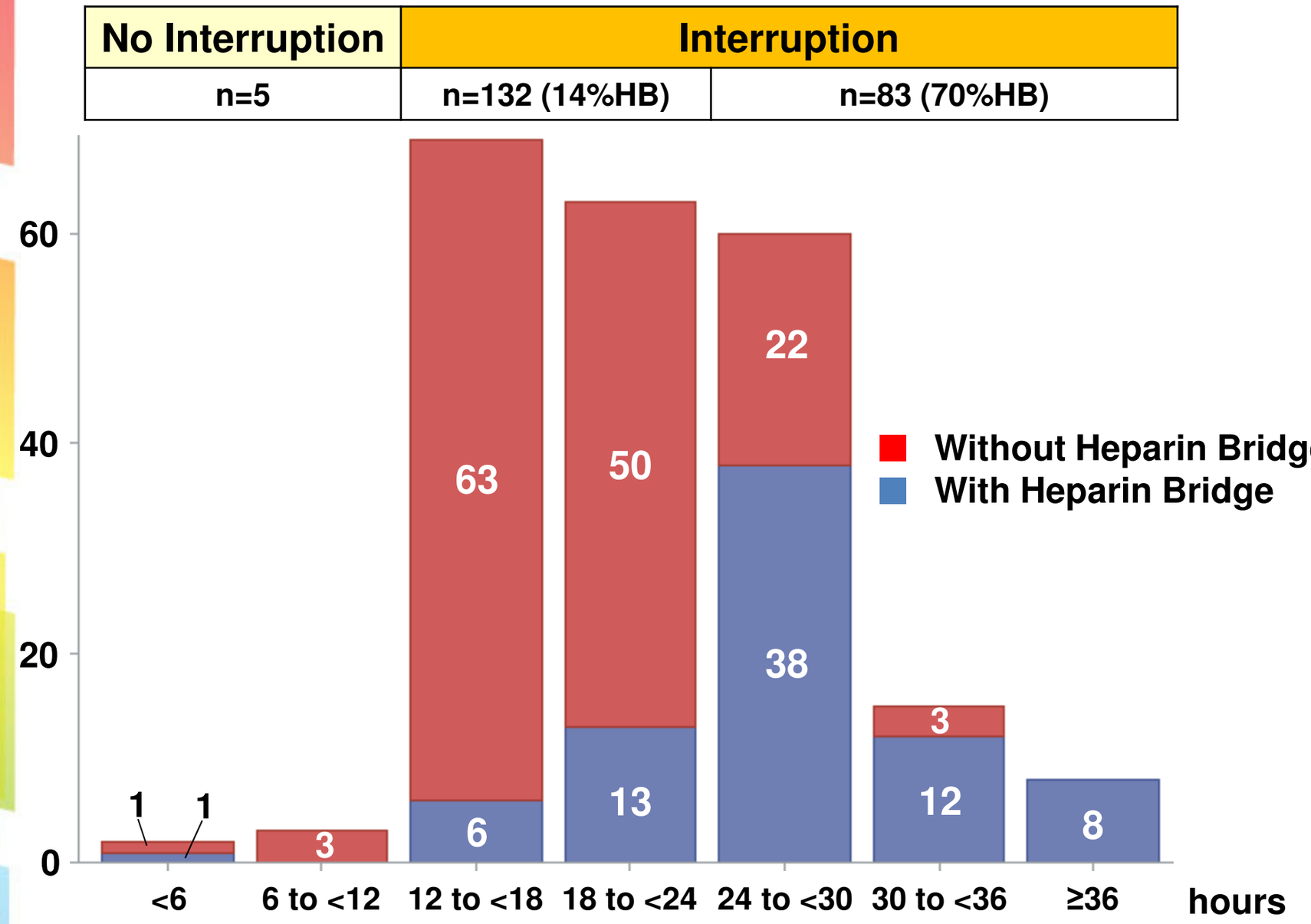
Interval between the Final Dose of Dabigatran and Ablation

The intervals between the final dose of dabigatran and the ablation (D-A interval) were <24 hours in 132 pts and heparin bridge was performed in 14%. The D-A intervals were ≥24 hours in 83 pts and heparin bridge was performed in 70%.



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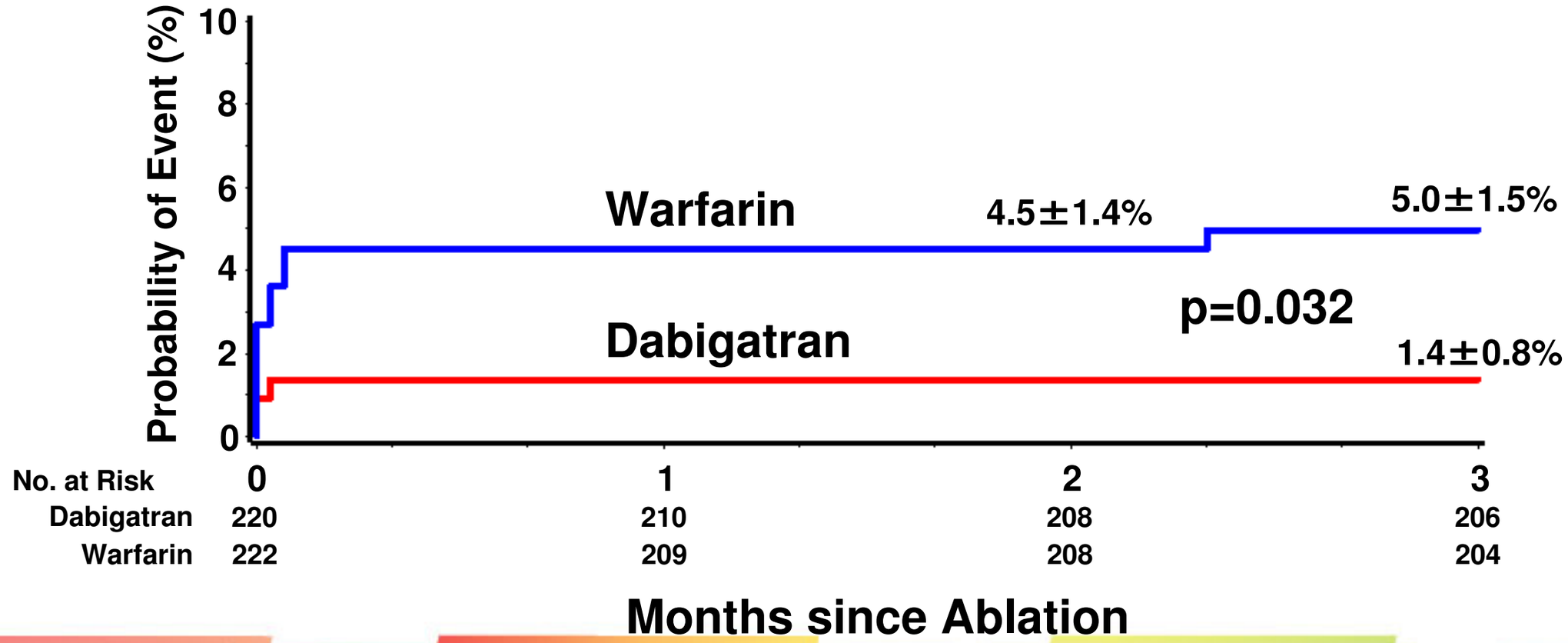
Major Bleeding Events and Ischemic Events during 3 Months

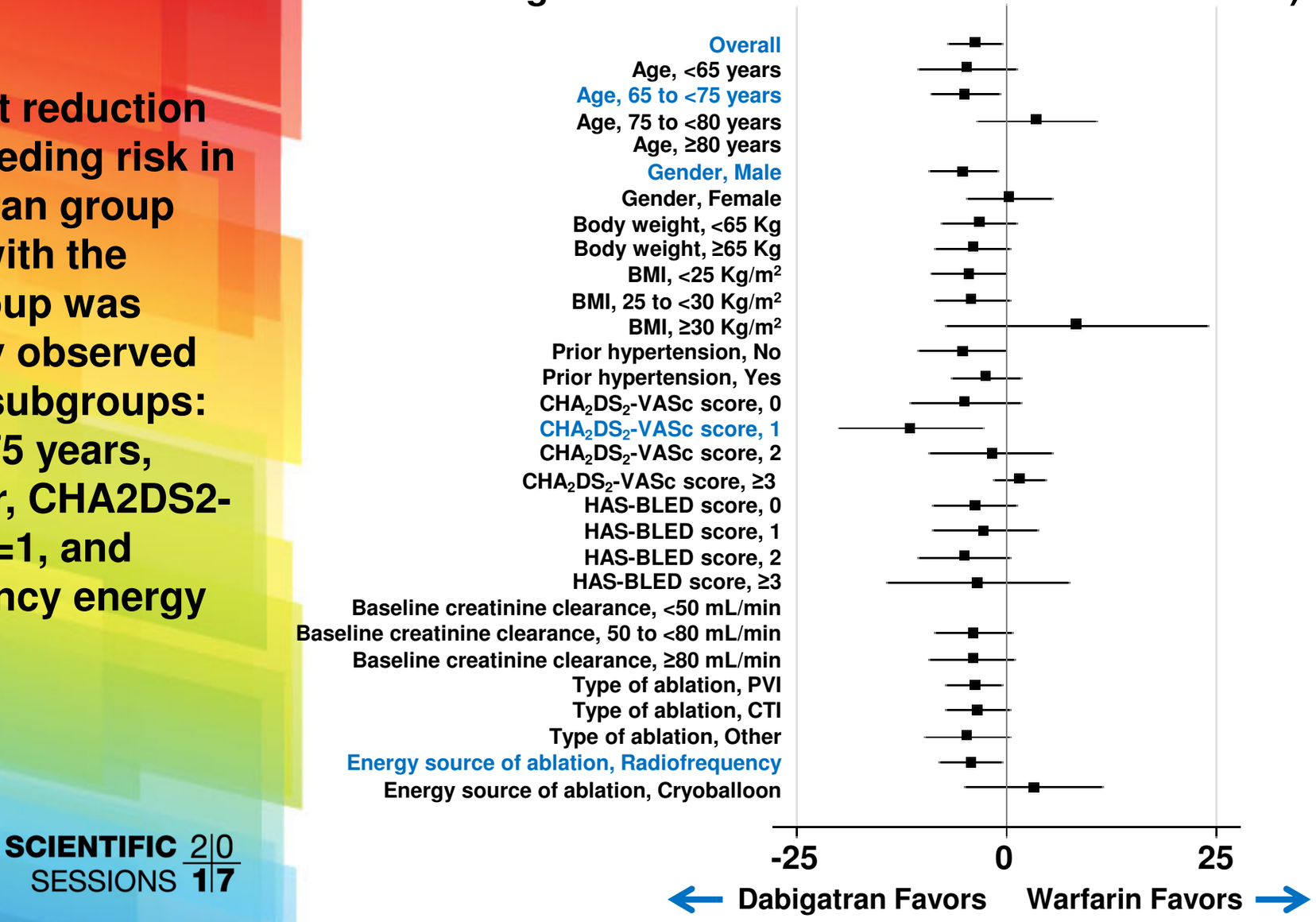
	Dabigatran (n=220)	Warfarin (n=222)
Cardiac tamponade, n	0	1 (0.5%)
Pericardial effusion, n	1 (0.5%)	0
Pericardial hemorrhage, n	0	2 (0.9%)
Groin bleeding/hematoma, n	0	3 (1.4%)
Femoral atrio-venous fistula, n	1 (0.5%)	1 (0.5%)
Femoral pseudoaneurysm, n	0	1 (0.5%)
Intraperitoneal bleeding, n	1 (0.5%)	0
Retroperitoneal bleeding, n	0	1 (0.5%)
Subcutaneous bleeding, n	0	1 (0.5%)
Compartment syndrome, n	0	1 (0.5%)
Total Major Bleeding Events, n	**3 (1.4%)**	**11 (5.0%)**
Cerebral infarction, n	0	1 (0.5%)
Total Ischemic Events, n	**0**	**1 (0.5%)**

Time to First Adjudicated Major Bleeding Event



Subgroup Analysis of the Incidence of Adjudicated Major Bleeding Events

A significant reduction in major bleeding risk in the dabigatran group compared with the warfarin group was consistently observed across the subgroups: age 65 to <75 years, male gender, CHA2DS2-VASc score=1, and radiofrequency energy ablation.



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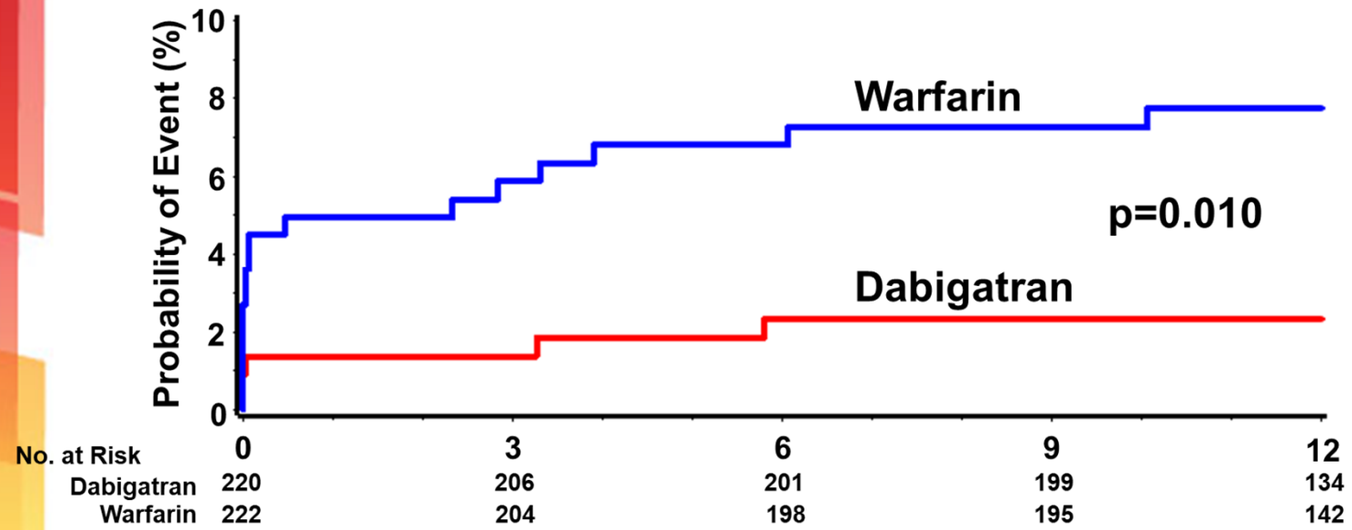
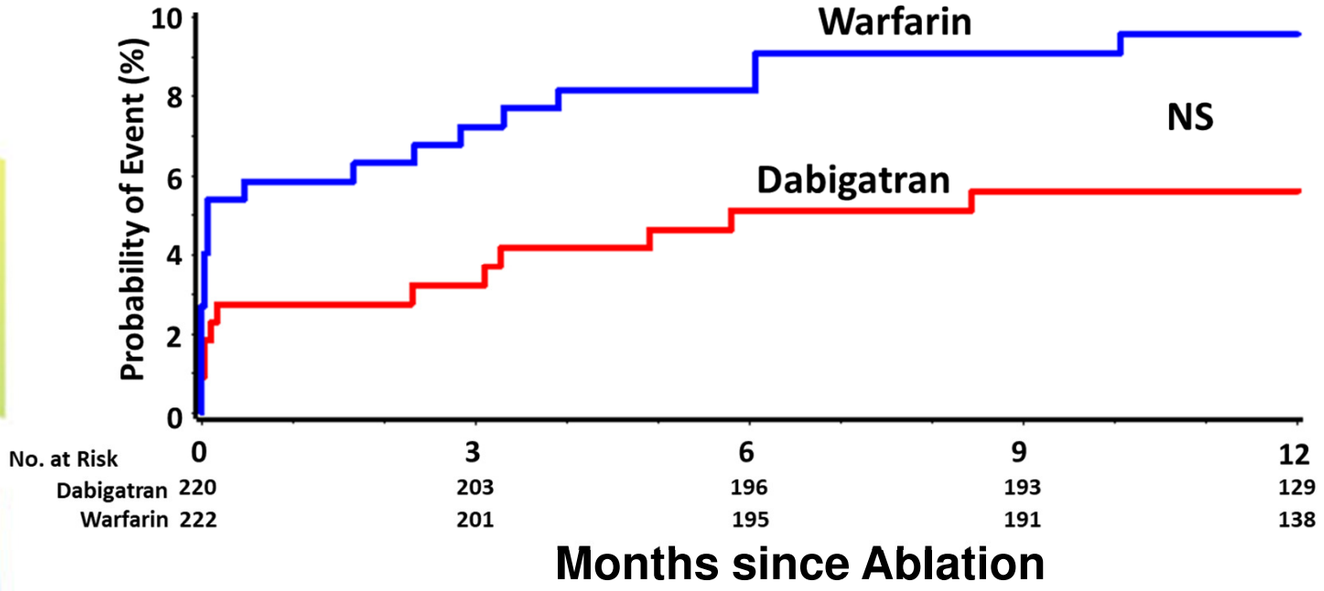
Composite Incidence (Major Bleeding and Thromboembolic Events)



Composite Incidence (All Bleeding and Thromboembolic Events)



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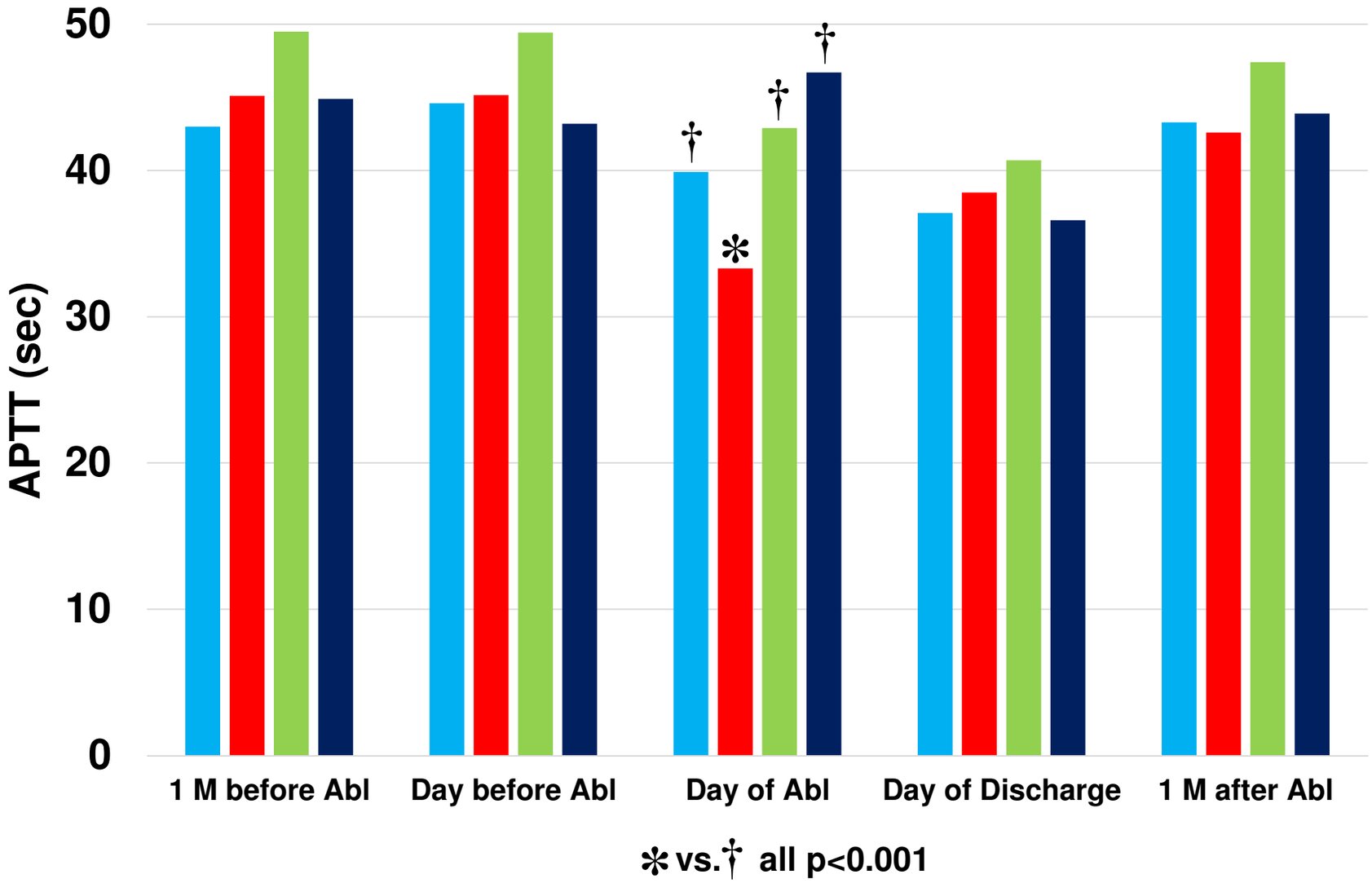
Interval of Dabigatran Interruption and APTT

D-A Interval

- <24 hours (without HB)
- ≥24 hours (without HB)
- <24 hours (with HB)
- ≥24 hours (with HB)



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Conclusions

In patients undergoing ablation for non-valvular atrial fibrillation, anticoagulation with minimally-interrupted dabigatran with or without heparin bridging was associated with fewer bleeding complications than uninterrupted warfarin with no increase in thromboembolic events.

ABRIDGE-J 28 Sites and Investigators

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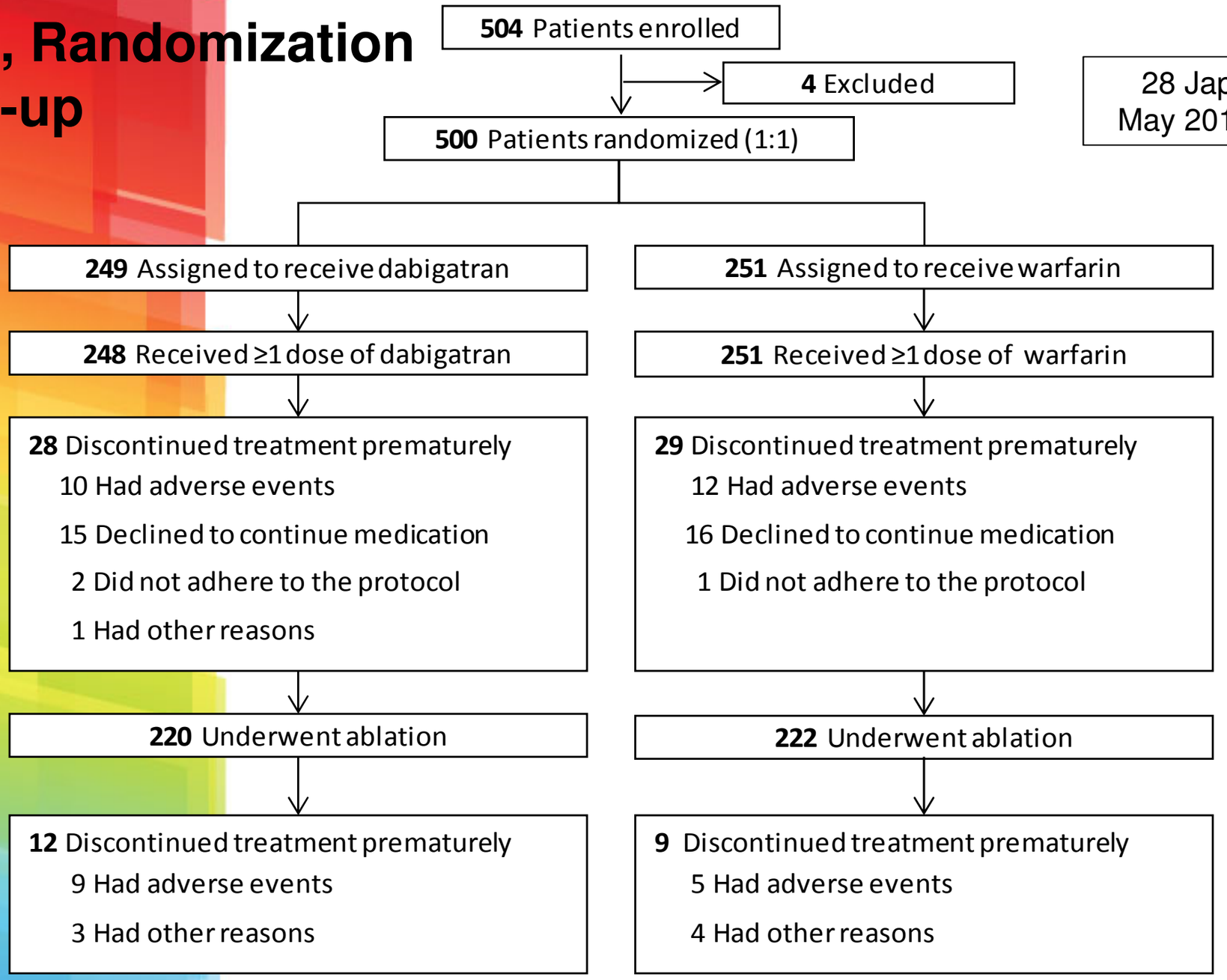
Fukushima Medical University: Dr. Takeishi.

Back-up Slides

Enrollment, Randomization and Follow-up



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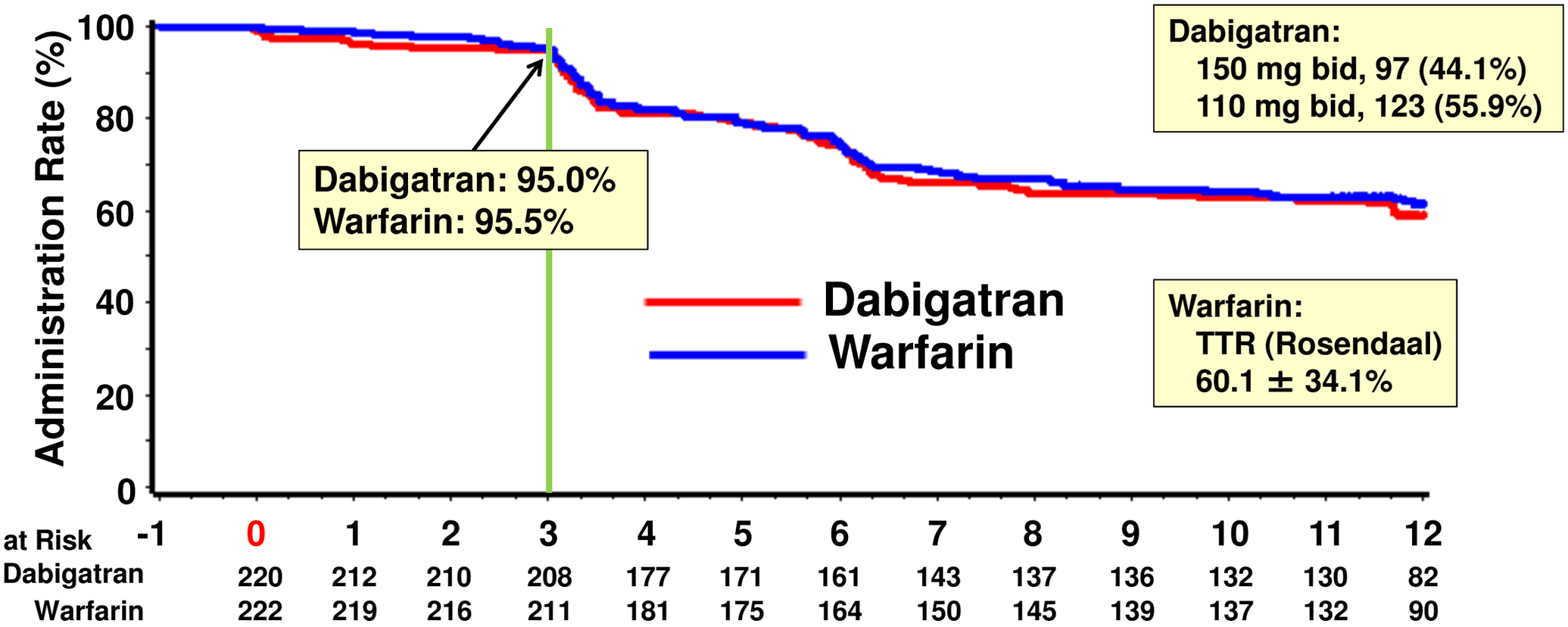
Anticoagulation Treatment and Adherence Rate



Months since Ablation

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Interval of Dabigatran Interruption and Anticoagulation

	Without Heparin Bridge			With Heparin Bridge		
	D-A Interval		p-value	D-A Interval		p-value
	<24 hours (n=117)	≥24 hours (n=25)		<24 hours (n=20)	≥24 hours (n=58)	
APTT, sec						
1 month before ablation	43.00 ± 9.83	45.08 ± 15.09	NS	49.48 ± 15.21	44.94 ± 10.04	NS
Day of ablation	39.92 ± 12.66	**33.26 ± 5.89**	**p<0.001**	42.93 ± 8.30	46.69 ± 23.33	NS
Day of discharge	37.14 ± 8.42	38.51 ± 14.09	NS	40.71 ± 8.52	36.63 ± 7.83	NS
1 month after ablation	43.25 ± 10.08	42.64 ± 7.13	NS	47.41 ± 11.61	43.86 ± 9.56	NS
D-dimer, μg/mL						
Day of discharge	0.51 ± 0.41	**0.87 ± 0.97**	NS	0.68 ± 0.40	0.57 ± 0.41	NS
	(0.0-2.0)	**(0.0-4.1)**		(0.0-1.3)	(0.0-1.8)	
1 month after ablation	0.32 ± 0.34	0.40 ± 0.28	NS	0.44 ± 0.21	0.38 ± 0.50	NS

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Comparison

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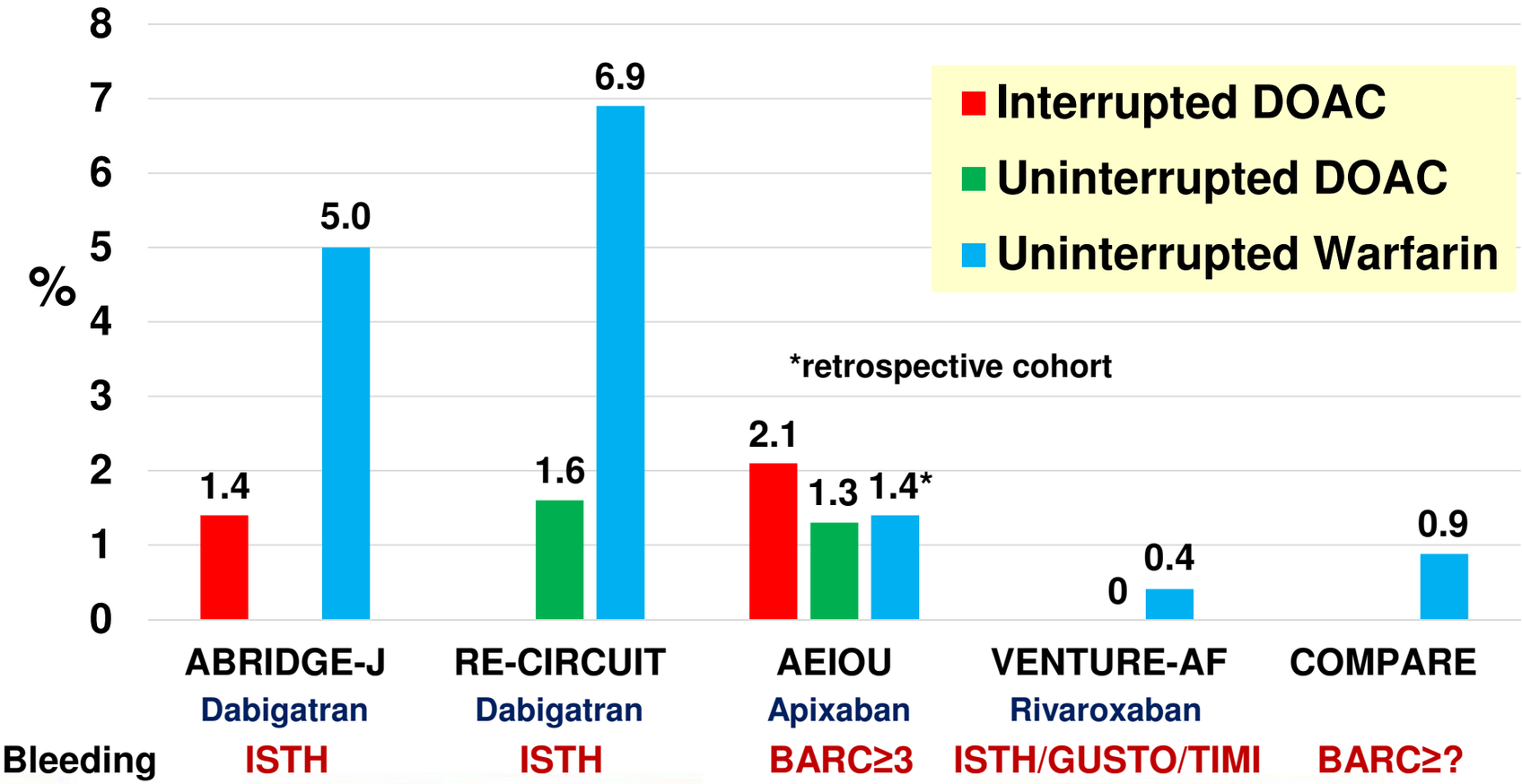
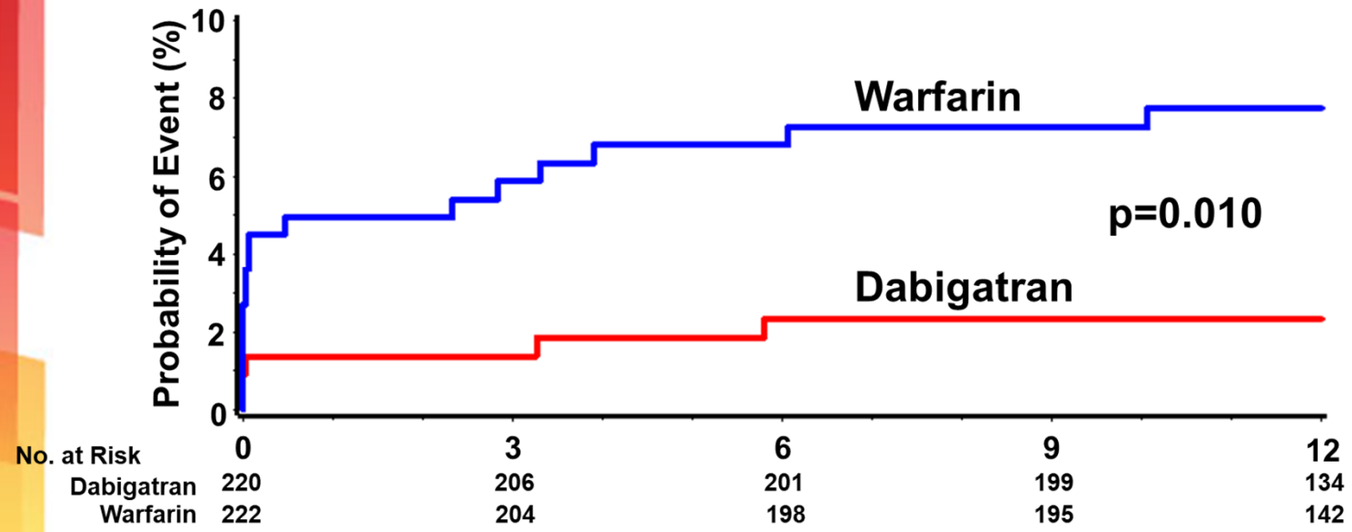
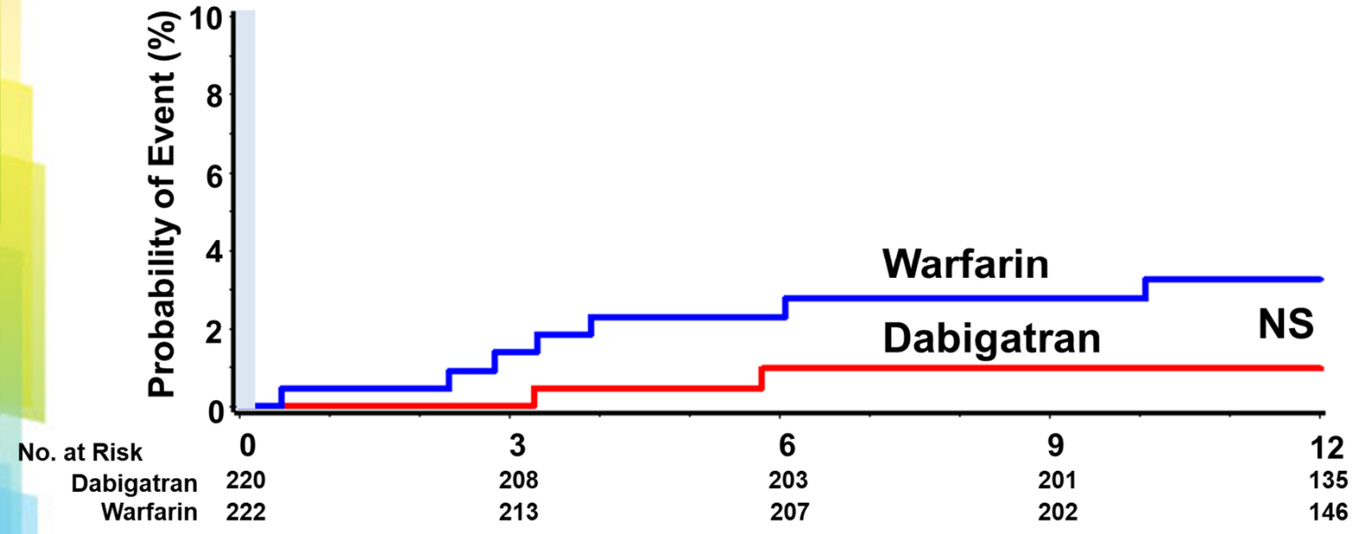
Major Bleeding



Composite Incidence (Major Bleeding and Thromboembolic Events)



Composite Incidence since Day 5 post Ablation



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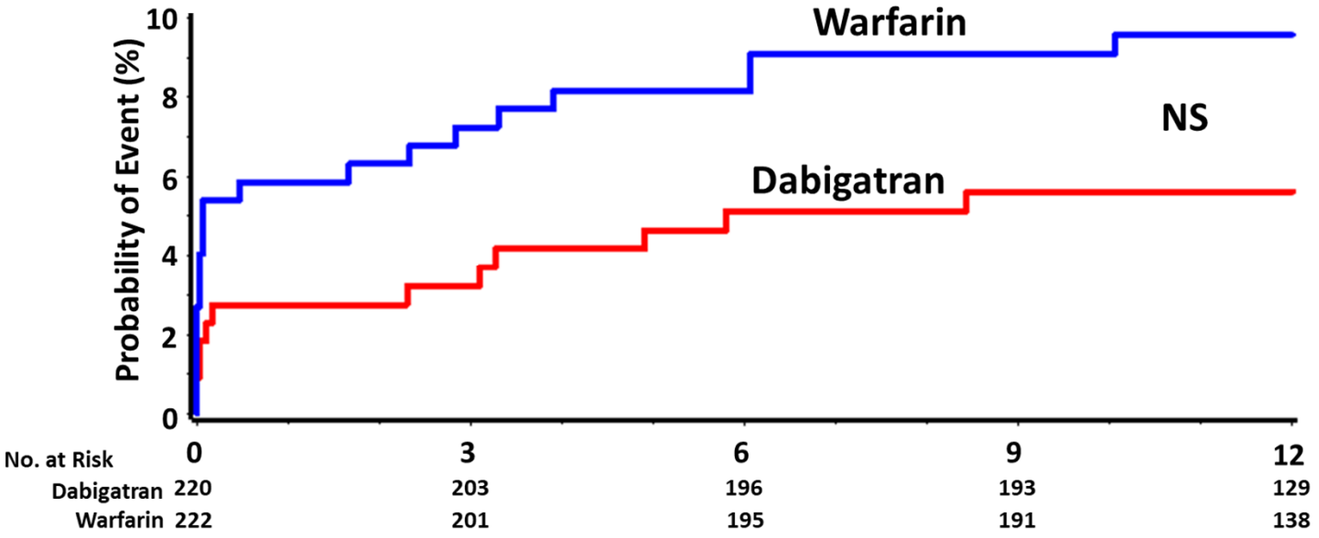
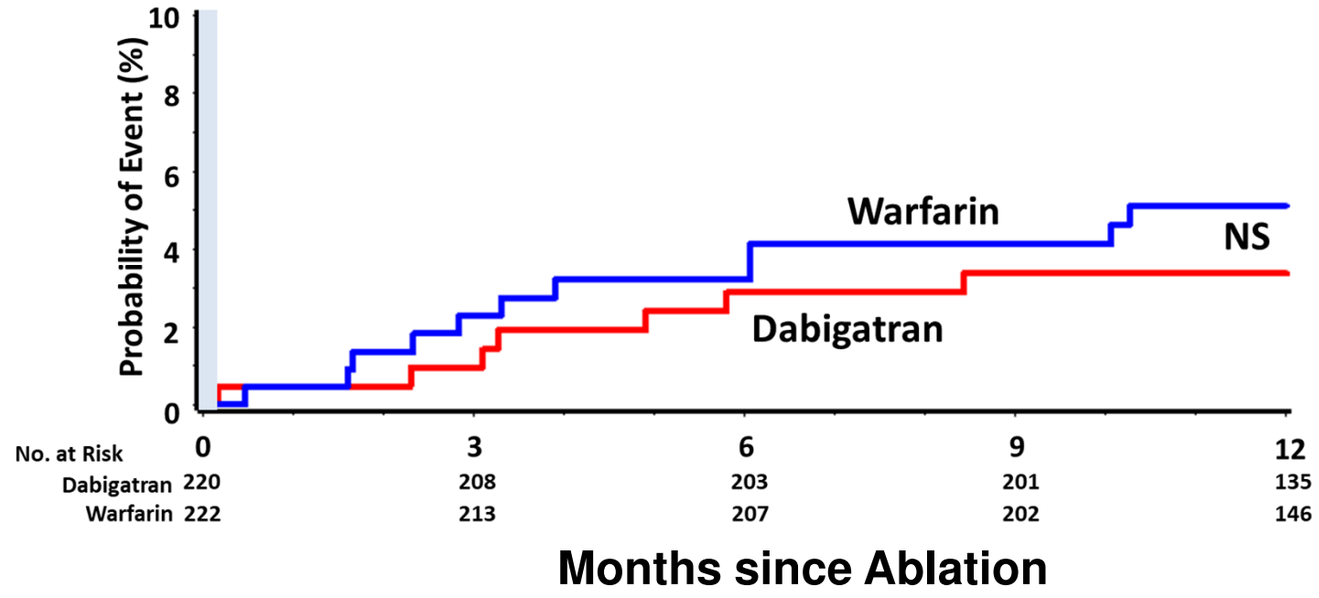
All Bleeding and Thromboembolic Events



All Bleeding and Thromboembolic Events since Day 5 post Ablation



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Procedural Characteristics in Patients with or without Major bleeding during 3 Months after Procedure

	Dabigatran (n=220)			Warfarin (n=222)		
	Major Bleeding (n=3)	No Major Bleeding (n=217)	p-value	Major Bleeding (n=11)	No Major Bleeding (n=211)	p-value
D-A interval <24 h without HB, n	0	117	-	N/A	N/A	-
D-A interval <24 h with HB, n	0	20	-	N/A	N/A	-
D-A interval ≥24 h without HB, n	3	22	-	N/A	N/A	-
D-A interval ≥24h with HB, n	0	58	-	N/A	N/A	-
APTT on day of ablation, sec	40.40 ± 12.45	41.10 ± 15.80	NS	47.83 ± 27.17	40.57 ± 9.83	NS
PT-INR on day of ablation (range)	0.965 ± 0.064	1.105 ± 0.107	NS	1.843 ± 0.383	2.064 ± 0.506	NS
	(0.92 - 1.01)	(0.94 - 1.58)		(1.29 - 2.46)	(1.08 - 3.99)	
Type of ablation						
RF PVI, n	2 (66.7%)	174 (80.2%)	NS	11 (100%)	160 (75.8%)	NS
Cryoballoon PVI, n	1 (33.3%)	33 (15.2%)	NS	0	44 (20.9%)	NS
Total heparin dose, IU	14560.0 ± 2207.9	14930.7 ± 6516.5	NS	7929.5 ± 3047.5	9634.6 ± 4216.5	NS
Protamine for reversal, n	3 (100.0%)	182 (83.9%)	NS	**5 (45.5%)**	**174 (82.5%)**	**p=0.0082**

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Baseline Characteristics in Patients with or without Major bleeding during 3 Months after Procedure

	Dabigatran (n=220)			Warfarin (n=222)		
	Major Bleeding (n=3)	**No Major Bleeding (n=217)**	p-value	**Major Bleeding (n=11)**	**No Major Bleeding (n=211)**	p-value
Age, years (range)	64.0 ± 10.1 (55 – 75)	63.8 ± 10.0 (30 – 85)	NS	62.3 ± 9.6 (40 – 73)	64.6 ± 9.8 (35 – 82)	NS
Body weight, Kg	67.20 ± 19.20	67.39 ± 11.82	NS	65.64 ± 11.97	66.01 ± 11.24	NS
Systolic blood pressure, mmHg	118.3 ± 7.8	130.4 ± 16.7	NS	138.2 ± 24.2	132.1 ± 17.7	NS
Creatinine clearance, mL/min	89.37 ± 25.80	83.58 ± 27.53	NS	84.01 ± 23.65	81.94 ± 25.06	NS
Paroxysmal AF, n	3 (100.0%)	135 (62.2%)	NS	4 (36.4%)	134 (63.5%)	NS
Diabetes mellitus, n	0	36 (16.6%)	NS	0	34 (16.1%)	NS
Hypertension, n	2 (66.7%)	121 (55.8%)	NS	5 (45.5%)	121 (57.3%)	NS
Alcohol abuse, n	0	2 (0.9%)	NS	**2 (18.2%)**	**2 (0.9%)**	**p=0.0127**
CHA_2DS_2-VASc score	2.3 ± 0.6	1.8 ± 1.5	NS	1.1 ± 0.7	1.9 ± 1.4	NS
HAS-BLED score	1.7 ± 1.2	1.3 ± 1.1	NS	1.5 ± 1.0	1.3 ± 1.0	NS
Labile INRs, n	0	20 (9.2%)	NS	2 (18.2%)	12 (5.7%)	NS
Antiplatelet use, n	0	19 (8.8%)	NS	2 (18.2%)	19 (9.0%)	NS
Dabigatran 150 mg twice, n	2 (66.7%)	95 (43.8%)	NS	N/A	N/A	-
Dabigatran 110 mg twice, n	1 (33.3%)	122 (56.2%)		N/A	N/A	-