Antithrombotic Treatment in patients with Effectively Maintained Sinus rhythm after Atrial Fibrillation ablation (ATEMS-AF)

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Korean Heart Rhythm Society

COI Disclosure

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Catheter ablation is an established rhythm-control therapy for symptomatic AF

- Proven to be superior to AAD in reducing AF recurrence, burden, and improving quality of life

The benefit of catheter ablation on stroke prevention remains uncertain.

- CABANA could not demonstrate lower risk of disabling stroke in catheter ablation compared to drug therapy

Table 2. Primary and Secondary Outcomes by Intention-to-Treat Analysis

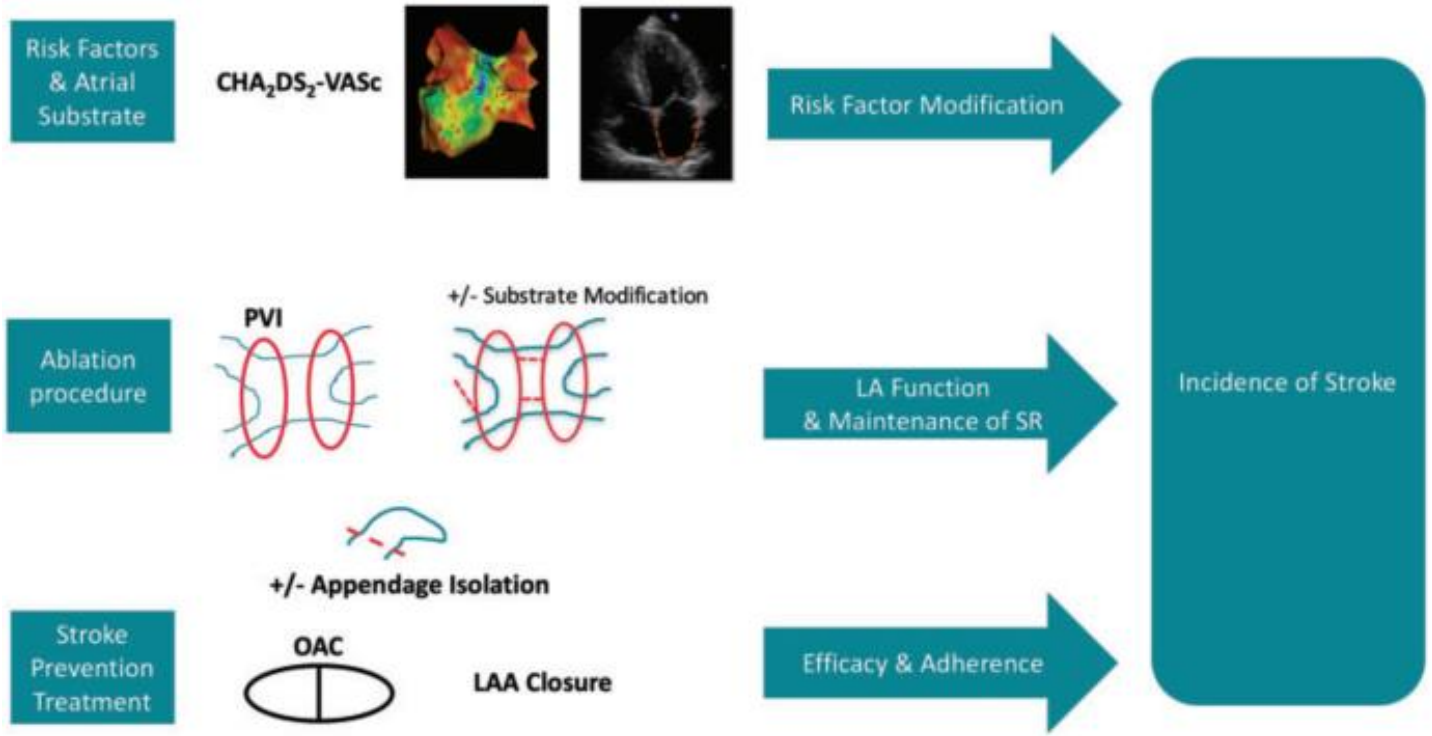
	Events, No. (%)		Kaplan-Meier 4-Year Event Rate, %				
	Catheter Ablation Group (n = 1108)	Drug Therapy Group (n = 1096)	Catheter Ablation Group (n = 1108)	Drug Therapy Group (n = 1096)	Absolute Reduction	Hazard Ratio (95% CI)[a]	*P* Value
Primary end point (death, disabling stroke, serious bleeding, or	89 (8.0)	101 (9.2)	7.2	8.9	1.7	0.86 (0.65-1.15)[c]	.30
Disabling stroke	3 (0.3)	7 (0.6)	0.1	0.7	0.6	0.42 (0.11-1.62)	.19
Serious bleeding	36 (3.2)	36 (3.3)	3.0	3.7	0.7	0.98 (0.62-1.56)	.93
Cardiac arrest	7 (0.6)	11 (1.0)	0.7	1.1	0.4	0.62 (0.24-1.61)	.33
Secondary end point							
Death or cardiovascular hospitalization	573 (51.7)	637 (58.1)	54.9	62.7	7.8	0.83 (0.74-0.93)	.001

The anticoagulation after catheter ablation?

Packer DL, et al.JAMA 2019; Asad ZUA, et al. Circ Arrhythm Electrophysiol 2019

Multiple factors play a role on a stroke risk (other than AF per se)

- It's not only the matter of "rhythm"
- Atrial myopathy, underlying risk factors, and altered left atrial function by ablation



Chew D, et al. Europace. 2021.

Optimal OAC therapy after catheter ablation?

- Guidelines:

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the EACTS[38]	'Long-term continuation of systemic anticoagulation beyond 2 months post-ablation is based on the patient's stroke risk profile and not on the apparent success or failure of the ablation procedure'.	Class I Level C
2018 CHEST Guideline and Expert Panel Report[39]	'In patients in whom sinus rhythm has been restored, we suggest that long-term anticoagulation should be based on the patient's CHA_2DS_2-VASc thromboembolic risk profile, regardless of whether sinus rhythm has been restored via ablation, cardioversion (even spontaneous), or other means'.	Weak recommendation, low-quality evidence
2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation	'Decisions regarding continuation of systematic anti-coagulation more than 2 months post-ablation should be based on the patient's stroke risk profile and not on the perceived success or failure of the ablation procedure'.[40]	Class I Level C
2014 Focused Update of the CCS Guidelines for Management of Atrial Fibrillation[41]	'AF ablation should not be considered as an alternative to oral anticoagulation. If a patient has a high thromboembolic risk profile (e.g., $CHADS_2$ risk score of ≥2), then the patient should continue oral anticoagulation even after successful AF ablation'.	NA
2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation[42]	'AF catheter ablation to restore sinus rhythm should not be performed with the sole intent of obviating the need for anticoagulation'.	Class III (Harm) Level C

"Based on the patients stroke risk profile"
"not depending on the success/failure of the ablation"

Hindricks G, et al. Eur Heart J 2021; Lip GYH, et al. Chest 2018; Calkins H, et al. Europace 2018

Concerns about OAC after catheter ablation

- Both early and late recurrence of AF is not uncommon
- Temporal association between AF episodes and stroke is not always apparent.

- Potential ***bleeding risk*** and more importantly,
- ***Patients' desire to discontinue OAC*** and willingness to take accept an increased risk of stroke.

Mahajan R, et al. Eur Heart J 2018; Brambatti M, et al. Circulation 2014

The aim of the study

- The **A**ntithrombotic **T**reatment in patients with **E**ffectively **M**aintained **S**inus rhythm after **A**trial **F**ibrillation ablation trial (**ATEMS-AF**)
- Compare antithrombotic strategies **after radiofrequency catheter ablation (RFCA) in patients with AF** of **CHA_2DS_2-VASc ≥ 2** and effectively maintained **sinus rhythm for at least 3 months.**

Method – Study design

- Investigator-initiated, prospective, randomized, multicenter, three-arm trial (pilot trial)
- February 2017 and March 2020
- 4 study sites
  - Seoul National University Hospital
  - Severance Cardiovascular Hospital
  - Korea University Guro Hospital, and
  - Korea University Anam Hospital

Method – Inclusion & Exclusion

Inclusion

- AF patients aged 20 years of older who underwent radiofrequency catheter ablation (RFCA)
- Effectively maintaining sinus rhythm for at least 3 months
- CHA_2DS_2-VASc ≥ 2

Exclusion

- Any recurrence of atrial tachycardia after RFCA
- VHD / HCM

Method – Study design

- 1:1:1
- **Aspirin 100mg or Clopidogrel 75 mg** (Group A) / **Edoxaban 30 mg** (Group B) / **Edoxaban 60 mg** (Group C)
- Assuming aspirin or clopidogrel is non-inferior to edoxaban 60mg in terms of the occurrence of stroke/TIA/TE
- 170 per group, followed up every 3 month

Method – Study outcomes

Primary outcomes

(1) The composite of any thrombotic and bleeding event

(2) Stroke/transient ischemic attack (TIA)/thromboembolism (TE)

(3) Major bleeding* and

(4) Non-major bleeding* at 24 months after randomization.

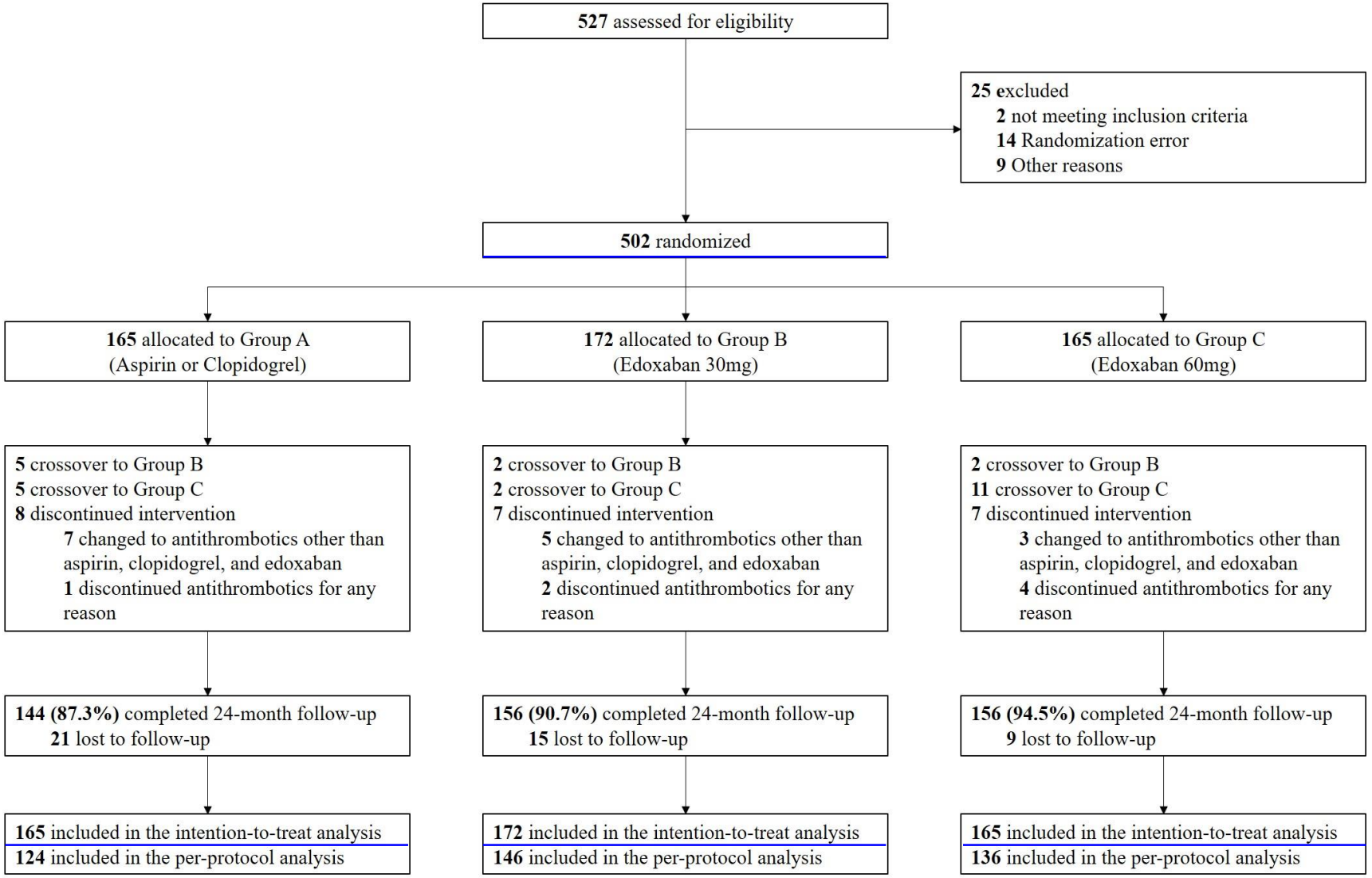
* the criteria ISTH released to AF and VTE in non-surgical patients

Secondary outcomes

(1) Any adverse event

(2) Recurrence of AF or atrial tachyarrhythmia (AT)

Results – Study population



Results – Baseline

- Mean age 67.3 years; Male 58.4%; Paroxysmal AF 60.4%; Mean CHA_2DS_2-VASc 2.8

	Total N=502	Group A N=165 (32.9%)	Group B N=172 (34.3%)	Group C N=165 (32.9%)	P-value
Age (years)	67.3 ± 7.8	67.0 ± 7.2	67.6 ± 7.7	67.4 ± 8.4	0.81
Male	293 (58.4%)	104 (63.0%)	99 (57.6%)	90 (54.5%)	0.28
BMI (kg/m^2)	25.0 ± 3.0	25.3 ± 3.0	24.9 ± 3.1	24.9 ± 2.9	0.41
Type of AF					0.18
Paroxysmal AF	303 (60.4%)	104 (63.0%)	110 (64.0%)	89 (53.9%)	
Persistent AF	140 (27.9%)	41 (24.8%)	48 (27.9%)	51 (30.9%)	
Long standing persistent AF	59 (11.8%)	20 (12.1%)	14 (8.1%)	25 (15.2%)	
Comorbidities					
HTN	404 (80.5%)	137 (83.0%)	134 (77.9%)	133 (80.6%)	0.49
DM	157 (31.3%)	56 (33.9%)	56 (32.6%)	45 (27.3%)	0.39
Stroke	57 (11.4%)	12 (7.3%)	25 (14.5%)	20 (12.1%)	0.10
CHF	79 (15.7%)	27 (16.4%)	29 (16.9%)	23 (13.9%)	0.74
Vascular disease	28 (5.6%)	13 (7.9%)	7 (4.1%)	8 (4.8%)	0.28
CHA_2DS_2-VASc score	2.8 ± 1.0	2.7 ± 0.9	2.9 ± 1.0	2.9 ± 1.1	0.40
History of smoking	118 (23.5%)	41 (24.8%)	44 (25.6%)	33 (20.0%)	0.43

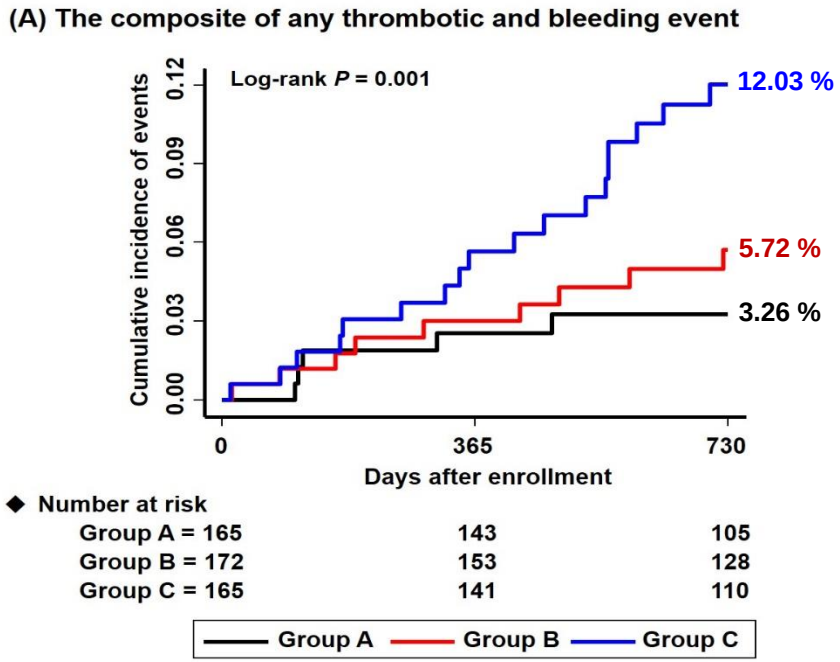
Results – Baseline

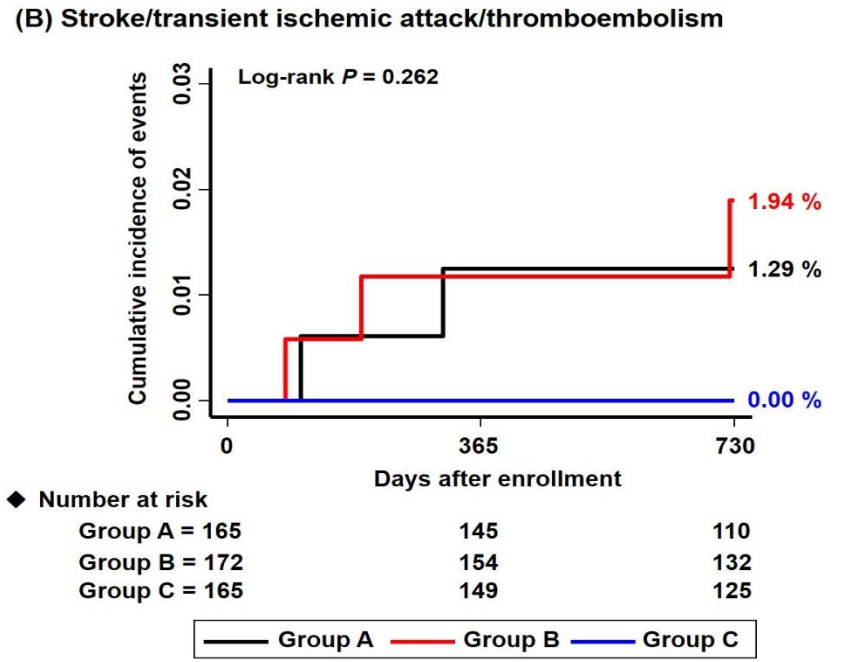
- LAD 40.9 mm; Duration from RFCA to enrollment 3.9 years

	Total N=502	Group A N=165 (32.9%)	Group B N=172 (34.3%)	Group C N=165 (32.9%)	P-value
Echocardiography					
LVEF (%)	58.5 ± 7.9	58.4 ± 8.1	58.7 ± 7.7	58.2 ± 8.1	0.85
LAD (mm)	40.9 ± 5.5	41.4 ± 5.6	40.6 ± 5.0	40.9 ± 5.7	0.40
E/E'	10.5 ± 4.2	10.2 ± 4.4	10.6 ± 4.0	10.8 ± 4.2	0.49
Laboratory values					
Bun (mg/dL)	16.4 ± 4.6	15.9 ± 4.3	16.5 ± 4.4	16.8 ± 5.1	0.22
Creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	0.57
TC (mg/dL)	172.6 ± 36.5	170.8 ± 37.1	172.8 ± 37.9	174.3 ± 34.5	0.68
LDL-C (mg/dL)	104.3 ± 33.3	100.9 ± 34.0	106.0 ± 34.7	105.9 ± 31.0	0.32
HDL-C (mg/dL)	50.0 ± 12.3	50.4 ± 13.1	48.5 ± 11.7	51.1 ± 11.9	0.17
TG (mg/dL)	129.4 ± 65.6	133.4 ± 74.6	123.8 ± 60.6	131.4 ± 61.0	0.41
BNP (pg/mL)	273.0 ± 380.5	278.0 ± 377.7	253.2 ± 391.4	288.0 ± 374.4	0.78
Statin use	147 (29.3%)	49 (29.7%)	42 (24.4%)	56 (33.9%)	0.16
RFCA~enrollment (days)	1407.5 (699.0-2093.0)	1680.0 (889.0-2303.0)	1297.5 (732.5-1883.0)	1189.0 (401.0-2004.0)	<0.001

Results – Primary outcomes

Group A: Aspirin or clopidogrel
Group B: Edoxaban 30 mg
Group C: Edoxaban 60 mg

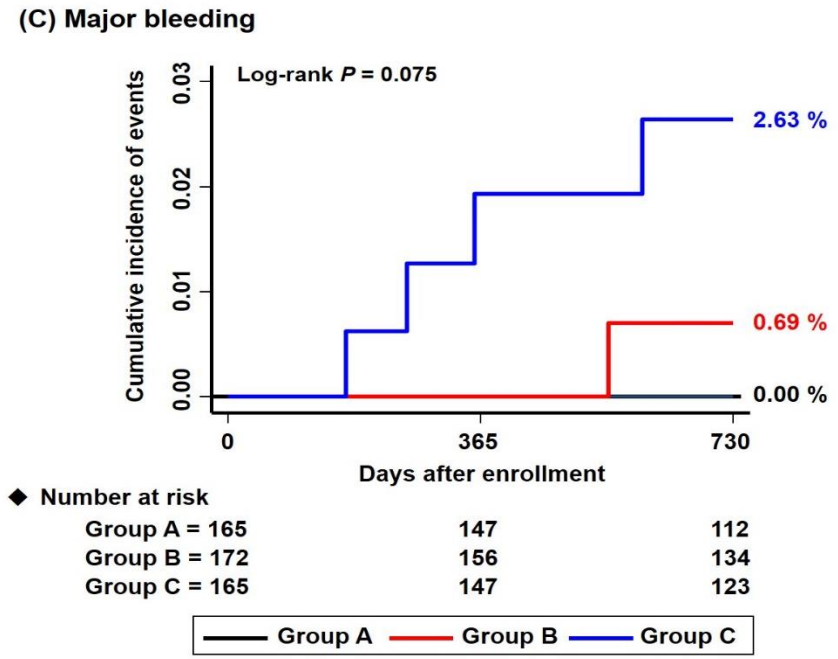


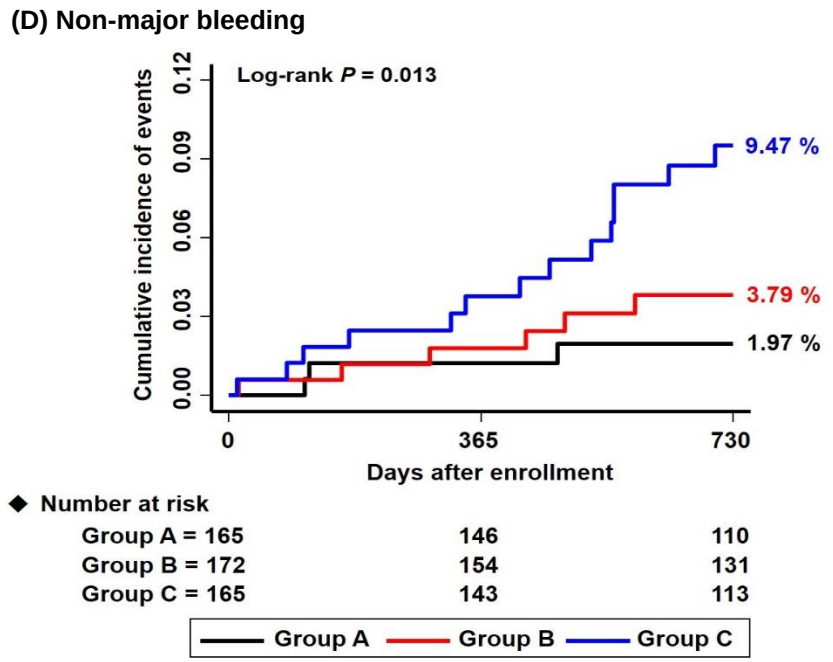


	Event / N	Cumulative incidence	HR (95% CI)	P value	HR (95% CI)	P value
The composite of any thrombotic and bleeding event						
Group A	5 / 165	3.26 %	1 (Reference)	-	0.282 (0.105-0.761)	0.012
Group B	9 / 172	5.72 %	1.666 (0.558-4.971)	0.360	0.471 (0.211-1.047)	0.065
Group C	18 / 165	12.03 %	3.541 (1.315-9.537)	0.012	1 (Reference)	-
Stroke/TIA/TE						
Group A	2 / 165	1.29 %	1 (Reference)	-	5.272 (0.429-727.231)	0.211
Group B	3 / 172	1.94 %	1.283 (0.250-7.704)	0.762	6.763 (0.656-909.362)	0.119
Group C	0 / 165	0.00 %	0.190 (0.001-2.332)	0.211	1 (Reference)	-

Results – Primary outcomes

Group A: Aspirin or clopidogrel
Group B: Edoxaban 30 mg
Group C: Edoxaban 60 mg





	Event / N	Cumulative incidence	HR (95% CI)	P value	HR (95% CI)	P value
Major bleeding						
Group A	0 / 165	0.00 %	1 (Reference)	-	0.116 (0.001-1.085)	0.061
Group B	1 / 172	0.69 %	2.766 (0.148-403.554)	0.505	0.320 (0.032-1.729)	0.194
Group C	4 / 165	2.63 %	8.631 (0.922-1143.736)	0.061	1 (Reference)	-
Non major bleeding						
Group A	3 / 165	1.97 %	1 (Reference)	-	0.217 (0.062-0.754)	0.016
Group B	6 / 172	3.79 %	1.853 (0.463-7.410)	0.383	0.402 (0.154-1.045)	0.062
Group C	14 / 165	9.47 %	4.615 (1.326-16.058)	0.016	1 (Reference)	-

Results – Detailed information on patients with stroke/TIA/TE

- The mean duration since RFCA=5.0 years; the mean CHA_2DS_2-VASc score=2.8
- The 3/5 had a prior history of stroke.
- One case reported a recurrence of AF after the occurrence of TIA.
- None of them experienced any bleeding events.

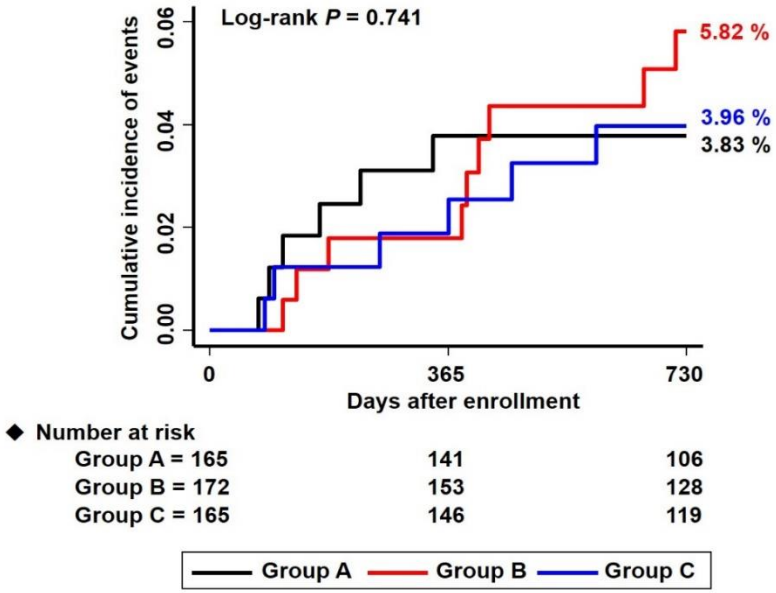
Group A: Aspirin or clopidogrel
Group B: Edoxaban 30 mg
Group C: Edoxaban 60 mg

N	Group	Age	Sex	BMI	CHA_2DS_2-VASc	Prior stroke	RFCA date	Enroll date	Stroke date	RFCA to stroke (days)	Stroke detail	Recurrence of AF	Any bleeding events
1	B	73	F	23.2	2	Yes	2016-03	2017-04	2019-04	1119	TIA	Not recurred	None
2	A	69	M	22.3	2	Yes	2011-03	2018-01	2018-11	2786	TIA	Recurred on 2020-01-13	None
3	B	76	F	23.1	3	No	2013-05	2018-03	2018-10	1953	Lt. PCA infarct	Not recurred	None
4	A	78	M	26.4	3	No	2009-11	2017-03	2017-07	2782	PTE after operation	Not recurred	None
5	B	64	F	28.3	4	Yes	2017-07	2018-09	2018-11	500	Rt. MCA infarct	Not recurred	None
					2.8	3/5				5.0 yrs		1/5	

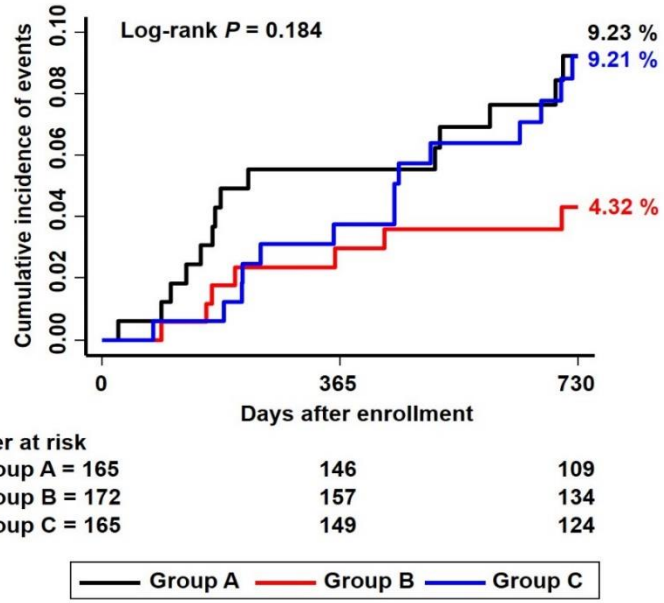
Results – Secondary outcomes

Group A: Aspirin or clopidogrel
Group B: Edoxaban 30 mg
Group C: Edoxaban 60 mg

(A) Adverse event



(B) Recurrence of atrial tachyarrhythmia



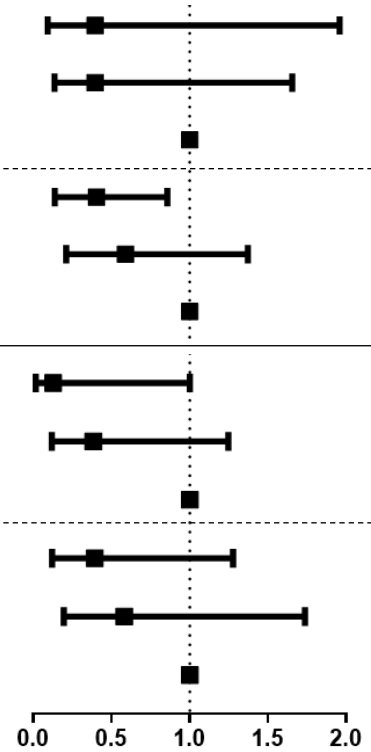
	Event / N	Cumulative incidence	HR (95% CI)	P value	HR (95% CI)	P value
Adverse event						
Group A	6 / 165	3.83 %	1 (Reference)	-	1.048 (0.338-3.249)	0.936
Group B	9 / 172	5.82 %	1.371 (0.488-3.853)	0.549	1.437 (0.511-4.037)	0.492
Group C	6 / 165	3.96 %	0.954 (0.308-2.960)	0.936	1 (Reference)	-
Recurrence of any atrial tachyarrhythmia						
Group A	14 / 165	9.23%	1 (Reference)	-	1.046 (0.499-2.195)	0.905
Group B	7 / 172	4.32%	0.458 (0.185-1.136)	0.092	0.480 (0.194-1.188)	0.112
Group C	14 / 165	9.21%	0.956 (0.456-2.005)	0.905	1 (Reference)	-

Results – Subgroup analyses

Group A: Aspirin or clopidogrel
Group B: Edoxaban 30 mg
Group C: Edoxaban 60 mg

- Composite outcome of any thrombotic and bleeding events

		Event / N	Cumulative incidence	HR (95% CI)	P value	HR (95% CI)	P value	P-for-interaction
Age < 65	Group A	2 / 53	4.14%	1 (Reference)	-	0.384 (0.074-1.979)	0.252	0.541
	Group B	1 / 50	2.00%	0.509 (0.046-5.611)	0.581	0.195 (0.023-1.671)	0.136	
	Group C	5 / 49	11.59%	2.606 (0.505-13.434)	0.252	1 (Reference)	-	
Age ≥ 65	Group A	3 / 112	2.84%	1 (Reference)	-	0.244 (0.069-0.855)	0.027	
	Group B	8 / 122	7.21%	2.349 (0.623-8.856)	0.207	0.572 (0.237-1.381)	0.214	
	Group C	13 / 116	12.15%	4.105 (1.170-14.406)	0.027	1 (Reference)	-	
RFCA – enrollment < 1459 days	Group A	1 / 74	1.49%	1 (Reference)	-	0.127 (0.016-1.001)	0.050	0.624
	Group B	4 / 100	4.42%	3.030 (0.339-27.108)	0.321	0.384 (0.118-1.247)	0.111	
	Group C	9 / 90	11.29%	7.889 (0.999-62.276)	0.050	1 (Reference)	-	
RFCA – enrollment ≥ 1459 days	Group A	4 / 91	4.71%	1 (Reference)	-	0.393 (0.121-1.277)	0.120	
	Group B	5 / 72	7.52%	1.481 (0.398-5.516)	0.558	0.582 (0.195-1.737)	0.332	
	Group C	9 / 75	12.83%	2.544 (0.783-8.262)	0.120	1 (Reference)	-	



group A did not show an increased risk of stroke/TIA/TE events compared to group B and C

Major findings

Group A: Aspirin or clopidogrel
Group B: Edoxaban 30 mg
Group C: Edoxaban 60 mg

- Group A did not show an increased risk of stroke/TIA/TE events compared to group B and C
- Group C showed an increased risk of primary outcomes, mostly driven by non-major bleeding events, compared to group A

- Overall, two-year cumulative incidences (incidence rate per 100 patients year):
  - 7.1% (3.91 per 100 patient years) for the composite of any thrombotic and bleeding event;
  - **1.1%** (**0.52** per 100 patient years) for **stroke/TIA/TE**;
  - **1.1%** (**0.52** per 100 patient years) for **major bleeding**; and
  - 5.1% (2.88 per 100 patient years) for non-major bleeding

An important medical challenge, areas of uncertainty

- The observational study in Denmark: **0.93-0.97** per 100 patient years among patients with CHA_2DS_2-VASc ≥ 2.
- The Chinese Atrial Fibrillation Registry: **0.69-1.11** per 100 patient years among patients with CHA_2DS_2-VASc ≥ 2 in men or ≥ 3 in women

- Similar rate with the major bleeding

Weighing stroke and bleeding risk is a challenge,
thus indicates that deciding OAC treatment after RFCA is a clinical equipoise

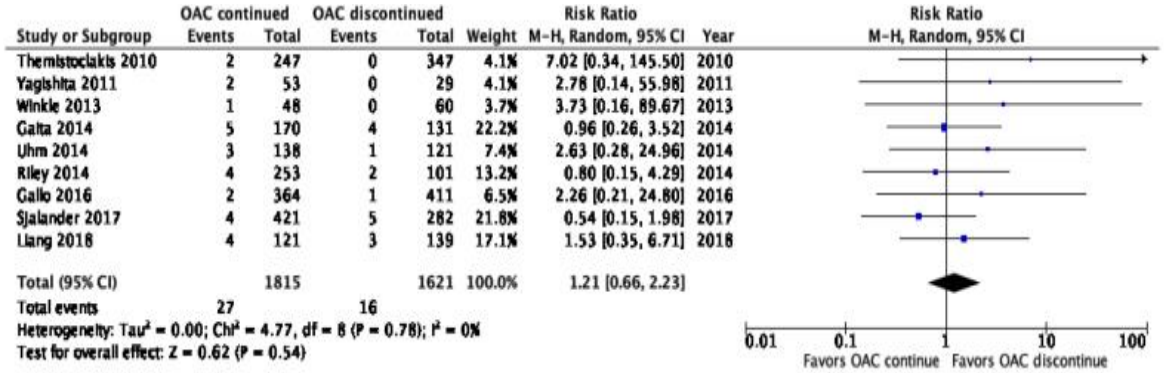
- Group C, highest non-major bleeding events

Continuing regular dose OAC in AF patients successfully maintaining sinus rhythm
could only make a nuisance bleeding events without evident benefits of preventing thromboembolic events

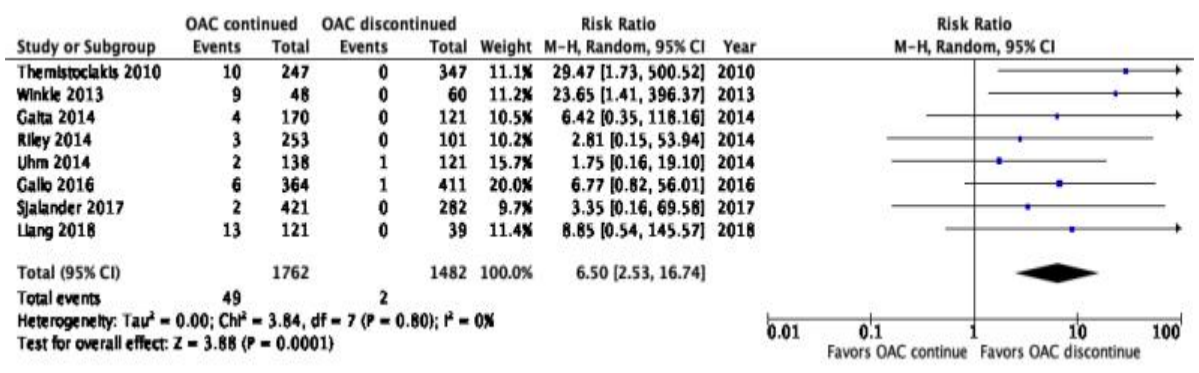
Favorable risk-benefit profile in OAC discontinuation

- Meta-analysis of 3,436 high-risk patients (CHADS2 or CHA_2DS_2-VASc ≥ 2)
- The effect of post-ablation anticoagulation;
- 6.5-hold higher risk of major bleeding in OAC continuation group with no difference in thromboembolic events.

- Systemic thromboembolism



- Major bleeding



Atti V, et al. J Atr Fibrillation 2018

Several concerns about post-ablation long-term anticoagulation.

Continuation

1) AF recurrence following ablation is common,
2) AF is not always temporaneously preceded by stroke
3) Less is known about the effect of AF ablation on the electrical and functional remodeling of LA, and
4) Not only the rhythm itself, but multiple underlying risk factors contribute to the incident stroke in AF

Discontinuation

1) The overall stroke risk in AF after catheter ablation is lower than expected,
2) The risk of bleeding and unfavorable effect on QOL are inevitable.
3) Certain patients are highly motivated to stop an anticoagulation even they have high risk of stroke profiles and willing to tolerate potential increased risk of stroke.

Nearly ***23%*** of moderate-high stroke risk patients are not remained on OAC following ablation.

Freeman JV, et al. Circ Arrhythm Electrophysiol 2019

Limitations

- The time from the catheter ablation to the enrollment varies with median 3.9 years

  → should be interpreted as a possible cessation of OAC in patients maintaining long-stable SR

- The history of antithrombotics between catheter ablation to the study enrollment

  → might affect the occurrence of thromboembolic or bleeding events.

- Follow-up by 12-lead ECG or Holter:

  → Paroxysmal event of AF might be not secured which necessitates the OAC

- Approximately 9% of patients were lost to follow-up

  → might alter the association between post-ablation anticoagulation and the study outcomes

Upcoming trials

Trial	Target enrolment	Enrolment criteria	Treatment groups	Primary outcome	Follow-up
OCEAN (NCT02168829)	1572	• Non-valvular AF • CHA_2DS_2VASc score ≥ 1 • ≥1 year post-successful AF catheter ablation without clinically apparent arrhythmia recurrence on serial 24-h Holter or an ECG monitoring	1. Rivaroxaban 15 mg daily 2. ASA 75–160 mg daily	Composite of stroke, systemic embolism, and covert embolic stroke on cerebral MRI	36 months
ODIn-AF (NCT02067182)	630	• Non-valvular symptomatic, paroxysmal or persistent AF • CHA_2DS_2VASc score ≥ 2 • Undergoing circumferential antral pulmonary vein ablation • Sinus rhythm (on 72-h Holter) following 3 months blanking period and 3 months observation period after ablation procedure • No clinical evidence of recurrent AF following 3 months blanking period and 3 months assessed by symptoms • No contraindications for OAC assessed by randomization of MRI of the brain	1. Dabigatran 150 mg b.i.d. (or 110 mg b.i.d. if age ≥ 75 years, CrCl 30–50 mL/min, concomitant verapamil use, increased bleeding risk) 2. No anticoagulation	New micro- and macro-embolic lesions on cerebral MRI incl. flare and diffusion weighted imaging at 12 months compared to baseline MRI (3 months after AF catheter ablation)	12 months

Chew D, et al. Europace. 2021

Conclusions

As a **post-ablation antithrombotics** strategy,

- ***No OAC*** (aspirin or clopidogrel) is associated with ***a lower risk of bleeding*** than edoxaban 60mg ***without difference in stroke prevention*** in patients with AF of CHA_2DS_2-VASc≥2 who underwent catheter ablation and effectively maintained sinus rhythm for at least 3 months.

- Whether successful ablation obviates the need for long-term anticoagulation remains uncertain and interplay of AF-stroke, underlying risk factors, and the outcome of catheter ablation should be comprehensively considered.

Thank you for your attention