The Role of Cardiologists in Stroke Prevention and Treatment

서울대병원 순환기내과 이소령



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Korean Heart Rhythm Society COI Disclosure

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The authors have no financial conflicts of interest to disclose concerning the presentation

Contents

- Case
- 2020 ESC Guidelines for AF management
 - CC to ABC

Case, 62/M

Height: 169 cm / Weight: 92.8 kg / BMI: 32.49 kg/m²

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Medical History>
# HTN on aspirin
# DM not on med
# Dyslipidemia
# BPH
```

Brief History>

본원 신환으로, 내원 6시간 전 발생한 Rt. Visual defect 을 주소로 5월 14일 7P경 응급실 내원함. 점심 식사 도중 오른쪽 시야가 잘 보이지 않았다고 하며, 외부병원 안과 가던 중 우측의 신호등이 시야에서 보이지 않았다고 함. 외부병원 안과 검진 이후 r/o stroke 으로 본원 응급실 refer 되었고, Acute stroke 확인되어 신경과 입원함.

Social history and previous medication

Social history

- Ex-smoker, 60 PY (quit 10YA)
- Current drinker, 소주 2병/주

Medication

- Aspirin protect 100mg 1T daily
- Pentoxifylline 400mg 1T daily
- Manidipine 10mg 1.5T daily
- Valsartan 80mg 1T daily
- Fenofibrate 160mg 1T daily
- Ursa 100mg 1T tid
- Finasteride 5mg 1T daily
- Tamsulosin 0.2mg 2T daily

Neurologic examination

Neurologic examination

MSE: alert, oriented to T/P/P

GCS: E4V5M6

Cranial nerve exam

L/R: 3mm/3mm, isocoric, prompt

EOM: full range without nystagmus

VF defect (+/-), Rt. hemianopsia,

V/A: no change

Facial expression : symm, intact

Facial sense : symm, intact

Tongue Deviation (-)

Dysarthria (-)

Nystagmus (-)

spontaneous (-)

gaze evoked nystagmus (-/-)

Motor

U/E: V/V

L/E: V/V

hand grip intact

Sensory: symmetrical, intact

DTR

Biceps: ++/++

Knee: ++/++

Toe sign: Equivocal

Cerebellar function test

No dysmetria on finger to nose

Vital sign and laboratory findings

157/98 - 60 - 18 - 36.7

BP fluctuation : maximum 174/98 - 58 - 18 - 36.9

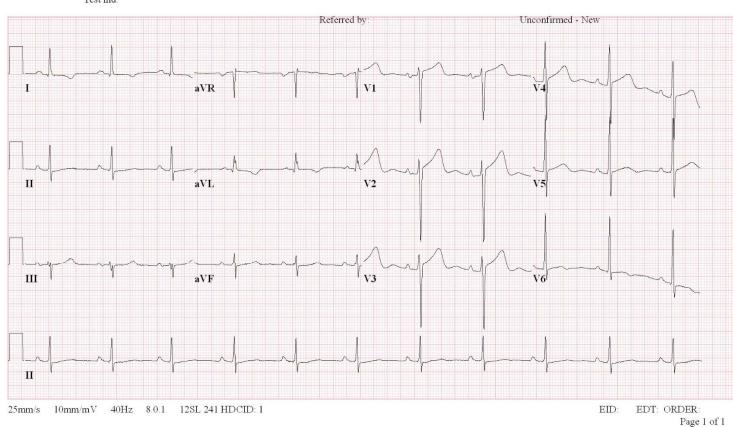
Fasting glucose 126~131 HbA1c 5.9

Total cholesterol 216 / TG 61 / HDL 60 / **LDL 153** BUN/Cr 20/0.94

ECG (2021/5/14)

Vent. rate	65 BPN	Λ	Normal sinus rhythm
PR interval	174 m	ıs	Minimal voltage criteria for LVH, may be normal variant
QRS duration	86 m	ıs	T wave abnormality, consider lateral ischemia
QT/QTc	452/470 m	IS	Prolonged QT
P-R-T axes	40 0 12	3	Abnormal ECG
	PR interval QRS duration QT/QTc	PR interval 174 m QRS duration 86 m QT/QTc 452/470 m	PR interval 174 ms QRS duration 86 ms QT/QTc 452/470 ms

Technician: Test ind:

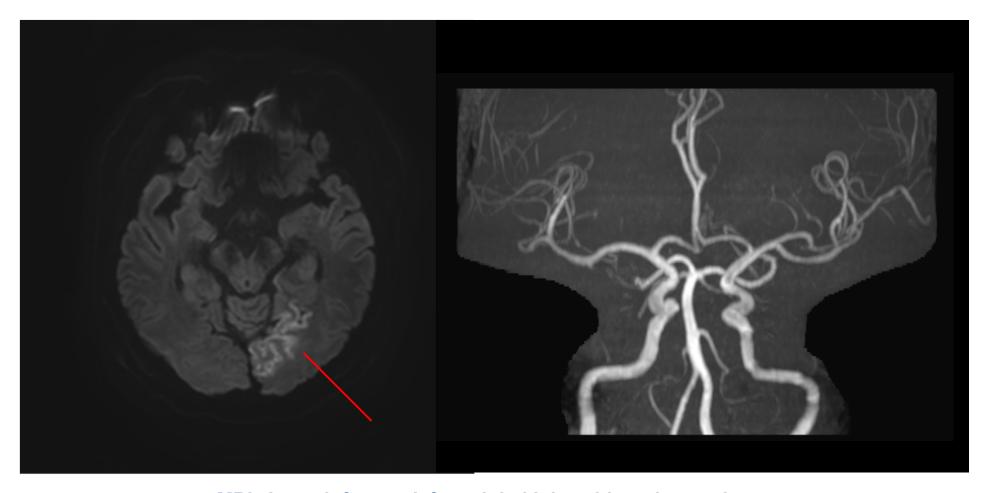


CT Brain perfusion (2021/5/14)



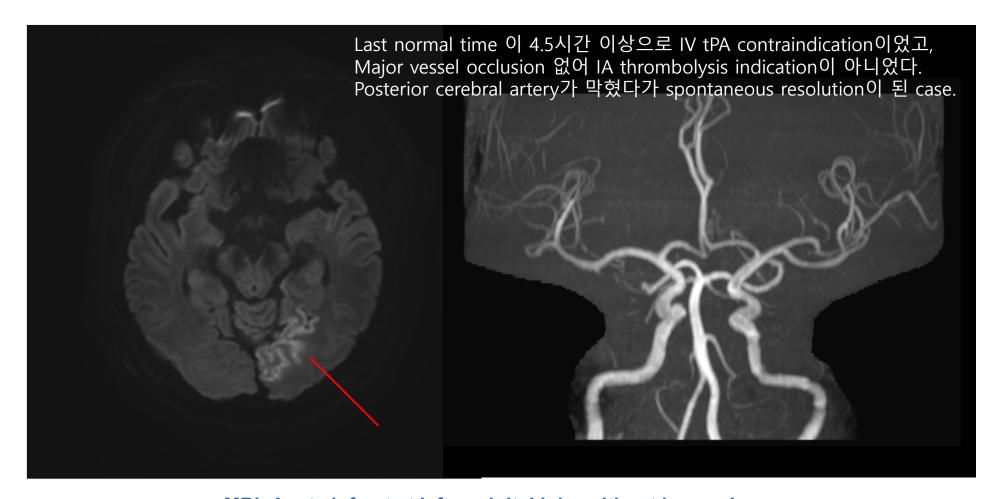
CT: Low density in left occipital lobe -> possible acute infarction CTA: No significant steno-occlusive lesion nor aneurysm in major intracranial and extracranial arteries

Brain MRI noncontrast (2021/5/14)



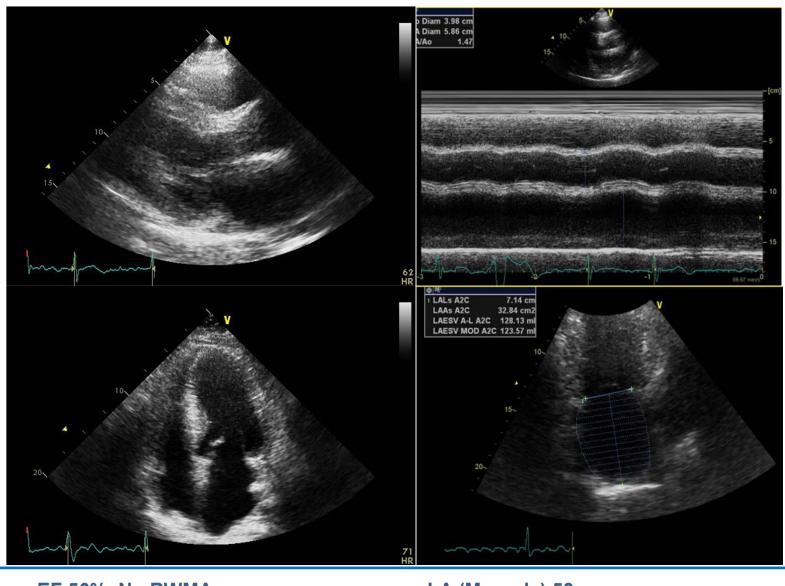
MRI: Acute infarct at left occipital lobe without hemorrhage MRA: No significant steno-occlusive lesion at both intracranial arteries

Brain MRI noncontrast (2021/5/14)



MRI: Acute infarct at left occipital lobe without hemorrhage MRA: No significant steno-occlusive lesion at both intracranial arteries

TTE (2021/5/17)



EF 56%, No RWMA Normal LV cavity size and valves

LA (M-mode) 58mm LA vol 124 ml, LAVI 59.3 ml/m²

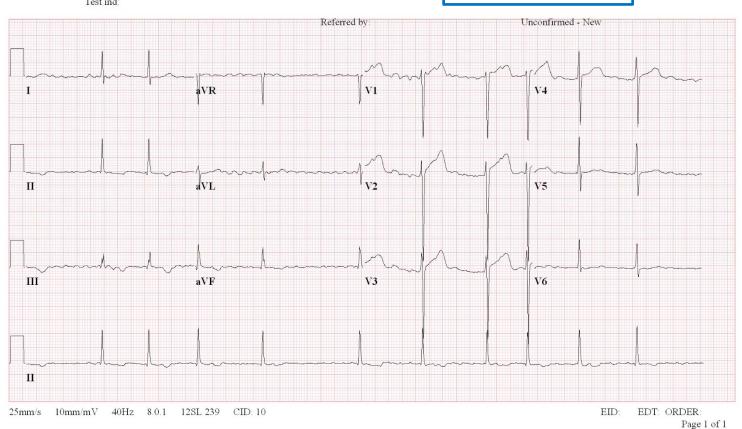
ECG (2021/5/17)

	Vent. rate	68	BPM
Male	PR interval	ak	ms
	QRS duration	80	ms
Room:	QT/QTc	370/393	ms
Loc:10	P-R-T axes	* 56	-56

Atrial fibrillation
Moderate voltage criteria for LVH, may be normal variant
T wave abnormality, consider inferior ischemia or digitalis effect
Abnormal ECG

Technician: Test ind:

Atrial Fibrillation



Holter (2021/5/20)

No AF/AFL

General

88086 QRS complexes

Ventriculars (V, F, E, I)

0 Bigeminal cycles

Runs totaling 0 beats

2867 Isolated 56 Couplets

2979 Ventricular beats (3%)
297 Supraventricular beats (< 1%)

< 1 % of total time classified as noise

Heart Rates

49 Minimum at 00:01:48 21-May

64 Average

116 Maximum at 07:44:32 21-May

5 Beats in tachycardia (>=100 bpm), < 1% total

32116 Beats in bradycardia (<=60 bpm), 36% total 1.68 Seconds Max R-R at 23:46:43 20-May

Supraventriculars (S, J, A)

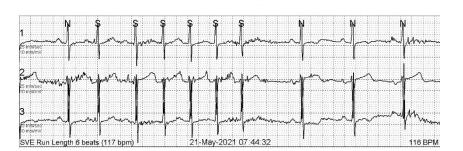
261 Isolated

8 Couplets

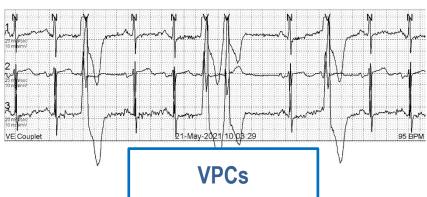
Bigeminal cyclesRuns totaling 20 beats

8 Beats longest run 109 bpm 08:35:06 21-May

3 Beats fastest run 118 bpm 17:34:24 20-May



Short run PAT



Hospital course

- 5/14 ER visit, Aspirin => DAPT
- 5/16 ECG monitoring 상에서 AF & AFL 관찰됨
- 5/17 A.fib 12 lead ECG documentation
- 5/19 DAPT => Xarelto
- ER 내원시에 비하여 주관적인 Rt. Visual field disturbance는 다소 호전되었음 (보이지 않는 분할선이 우측으로 이동).
- RUQ의 finger count는 여전히 안되고 있음.

Cardiology consultation:

안녕하십니까 교수님

상기 환자 Lt. PCAt infarction with newly documented A.fib으로 본과 입원하고 있습니다. 내원 당시 NSR에 frequent APC, VPC 있었으나 stroke unit 에서 continuous monitoring 시 확인하였을 때 5/16 오후부터 AF with A.flutter 로 리듬 변하여 5/17 monitoring off 할 때까지지속되었습니다. HTN, DL, obesity 의 risk factor 있던 환자입니다.

Echocardiography 결과 EF 56%, No RWMA이며 LAVI 59.3 mL/m2 으로 LA가 확장되어 있습니다. Rate는 50-80회 /분으로 현재 rate control 필요성은 없을 것으로 생각되며, 금-토 holter 이후 퇴원 예정으로 A.fib burden 확인할 예정입니다. 환자 나이 아직 고령은 아니고 A.fib 이 paroxysmal 하게 발생한 것이라면 rhythm control 의 candidate가 될 수도 있으리라 사료됩니다. Holter 결과는 퇴원 이후 확인할 예정으로 신경과 및 귀과 외래 함께 f/u 해도 될지 여쭙습니다. 바쁘신 와중 대단히 감사합니다.

NR R2 000 배상

Discharge record and medication

Summary

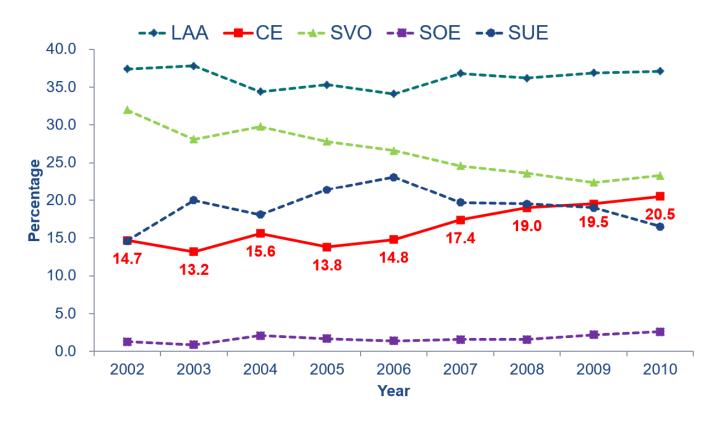
- Left PCA territory infarction
- Sx: Rt. Hemianopsia
- Risk factor: HTN, DL, obesity, exsmoker, newly documented AF
- Mechanism: CE
- Med: ASA->DAPT->NOAC
- Initial NIHSS 1

Medication

- Rivaroxaban 20mg 1T daily
- Atorvastatin 20mg 1T daily
- Famotidine 20mg 1T daily
- Amlodipine 5mg 1T bid
- Valsartan 80mg 1T daily
- Fenofibrate 160mg 1T daily
- Ursa 100mg 1T tid
- Finasteride 5mg 1T daily
- Tamsulosine 0.2mg 1T daily

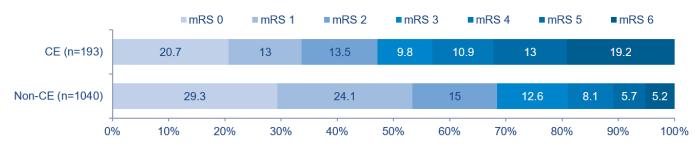
Cardioembolic stroke has increased in Korea

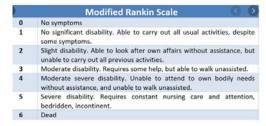
Korean Stroke Registry (n=46,098)

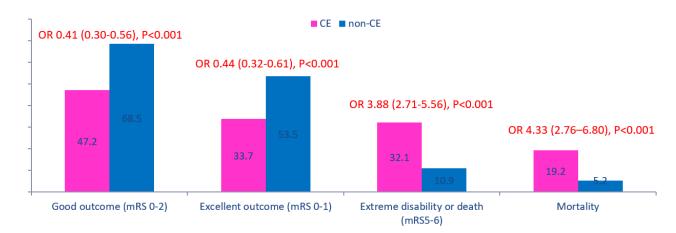


CE stroke is more disabling and more fatal

3-month mRS outcome: COMPASS registry (n=1233) 4 university hospitals for one year (2006)

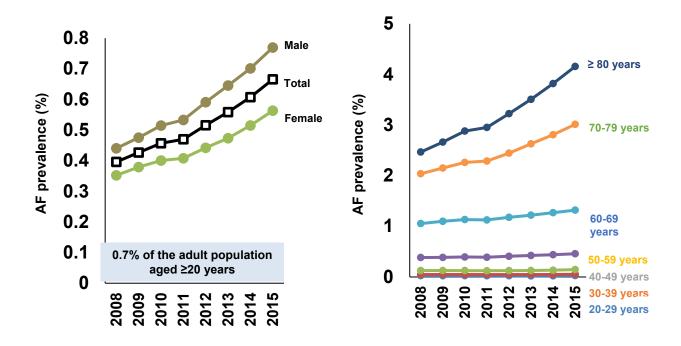






심방세동 유병률은 지속적으로 증가 추세

- 2008년에 비해 2015년에 심방세동 유병률은 2배 증가
- 20015년 기준 80세 이상 환자는 AF유병률이 4.16%



심방세동으로 인한 입원, 이로 인한 healthcare cost도 증가 추세

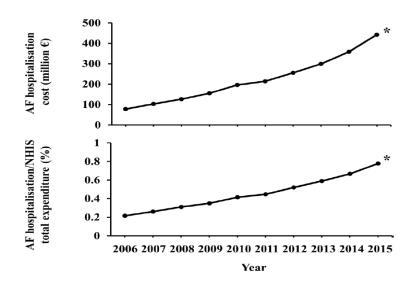
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	P value for trend
Total Korean AF population, n	269 448	315 854	359695	402 024	442 657	481 682	520 070	558 651	598 614	639 349	
Patients with hospitalisations, n (%)	16639 (6.2)	20539 (6.5)	24 948 (6.9)	28345 (8.2)	33214 (7.1)	36 025 (7.5)	41 421 (8.0)	46 012 (8.2)	51 223 (8.6)	58160 (9.1)	<0.001

Hospitalization % 6.2% → 9.1%

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Relative increase*, %	P value for trend
Overall	767	997	1275	1529	1854	2048	2497	2914	3397	3986	420	< 0.001

Hospitalization
Relative increase 420%

Temporal trends of medical cost between 2006 and 2015



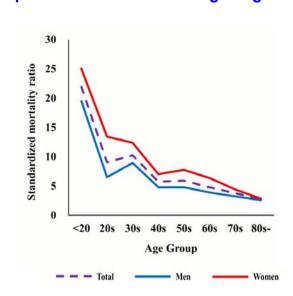
심방세동 환자들이 응급실을 방문하는 가장 흔한 원인은 뇌졸중

2006 (n=62,781)	2007 (n=69,781)	2008 (n=75,806)	2009 (n=83,721)	2010 (n=93,102)	2011 (n=97,903)
8.7 Cerebral infarction	9.7 Cerebral infarction	9.9 Cerebral infarction	9.3 Cerebral infarction	9.1 Cerebral infarction	9.3 Cerebral infarction
6.3 Atrial fibrillation	7.3 Atrial fibrillation	7.4 Atrial fibrillation	7.5 Atrial fibrillation	7.3 Atrial fibrillation	8.3 Atrial fibrillation
4.4 Angina	5.1 Angina	4.7 Heart failure	4.6 Angina	4.7 Heart failure	4.5 Heart failure
3.8 Heart Failure	4.5 Heart Failure	4.6 Angina	4.5 Heart failure	4.2 Angina	3.9 Angina
3.1 AMI	3.1 AMI	2.6 Pnemonia	2.9 Pnemonia	3.1 Pnemonia	3.3 Pnemonia
1.8 Pneumonia	2.3 Pneumonia	2.4 AMI	2.0 AMI	1.9 CKD	1.9 CKD
1.7 COPD	1.9 COPD	1.8 CKD	1.8 CKD	1.7 AMI	1.6 AMI
1.5 CKD	1.7 CKD	1.8 COPD	1.6 Lung cancer	1.7 Lung cancer	1.6 Gastroenteritis
1.3 ICH	1.6 Lung cancer	1.6 Lung cancer	1.5 COPD	1.5 Gastroenteritis	1.6 Lung cancer
1.2 Lung cancer	1.3 Intracranial injury	1.3 Fracture of femur	1.4 Fracture of femur	1.5 Fracture of femur	1.4 COPD
2012 (n=111,101)	2013 (n=116,102)	2014 (n=130,441)	2015 (n=144,724)	2016 (n=169,678)	2017 (n=159,004)
8.8 Cerebral infarction	8.8 Cerebral infarction	8.5 Cerebral infarction	8.0 Cerebral infarction	7.6 Cerebral infarction	8.9 Atrial fibrillation
8.2 Atrial fibrillation	8.0 Atrial fibrillation	8.1 Atrial fibrillation	7.7 Atrial fibrillation	7.5 Atrial fibrillation	8.4 Cerebral infarction
4.4 Heart Failure	4.4 Heart Failure	4.5 Heart failure	4.4 Heart failure	4.6 Heart failure	5.5 Heart failure
3.9 Angina	3.9 Angina	3.7 Angina	4.0 Pneumonia	3.9 Pneumonia	4.7 Pneumonia
3.8 Pneumonia	3.6 Pneumonia	3.6 Pneumonia	3.6 Angina	3.5 Angina	4.2 Angina
2.0 CKD	2.1 CKD	2.0 CKD	2.0 CKD	2.1 Gastroenteritis	2.6 Gastroenteritis
1.7 Gastroenteritis	2.0 Gastroenteritis	1.8 Gastroenteritis	1.9 Gastroenteritis	1.9 Dizziness	2.4 Dizziness
1.5 Dyspnea	1.5 Dizziness	1.6 Dizziness	1.6 Dyspnea	1.7 CKD	2.1 CKD
1.4 Intracranial injury	1.4 Dyspnea	1.5 Dyspnea	1.6 Dizziness	1.3 Abdominal pain	1.7 Fracture of femu
1.4 AMI	1.4 AMI	1.4 AMI	1.4 Intracranial injury	1.3 Fracture of femur	1.6 Abdominal pain

심방세동은 모든 사망, 심뇌혈관 사망 위험을3.7배, 5배 증가 시킴

- Patients with AF had a 3.7-fold increased risk of all-cause death and a 5-fold increased risk of CV death compared with the general population.
- The standardized mortality ratio for all-cause death was the highest in young patients and decreased with increasing age.
- CV disease was the leading cause of death and cerebral infarction was the most common cause as a specific disease.

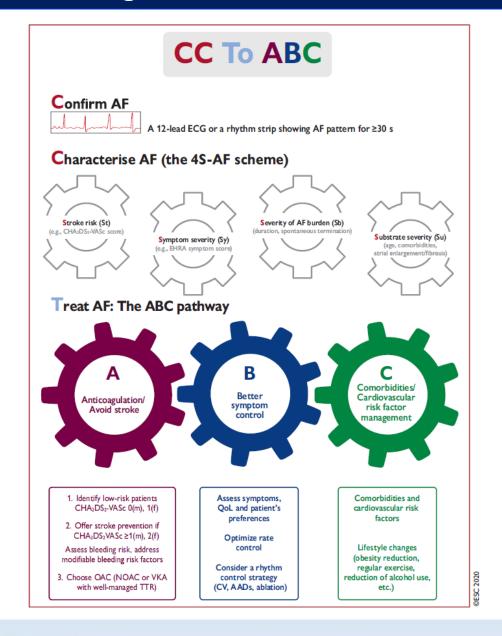
Standardized mortality ratios of patients with AF according to age



Cause of death

Rank	AF pa	tients		
	ICD-10 codes		Number (%)	
1	Diseases of the circulatory system (I)		1,701 (38.0)]
2	Malignant neoplasms (C)		1,046 (23.4)	
3	Diseases of the respiratory system (J)		372 (8.4)	
4	Symptoms, signs and abnormal clinical not elsewhere classified (R)	and laboratory findings,	275 (6.2)	
5	Endocrine, nutritional and metabolic d			Death
6	Injury, poisoning and certain other cor causes (S & T)	Diseases of the circulato		1,701 (38.0)
7	Diseases of the digestive system (K)	Cerebrovascular disea	STORE MET IN PRODUCT	732 (16.3)
8	Diseases of the genitourinary system (N	Ischemic heart disease		368 (8.2)
9	Certain infectious and parasitic disease	Hypertensive diseases	(I10-3)	151 (3.4)
	Diseases of the nervous system (G)	Heart failure (I50)		145 (3.2)
10	Diseases of the nervous system (G)	Other circulatory dise	ases	305 (6.8)

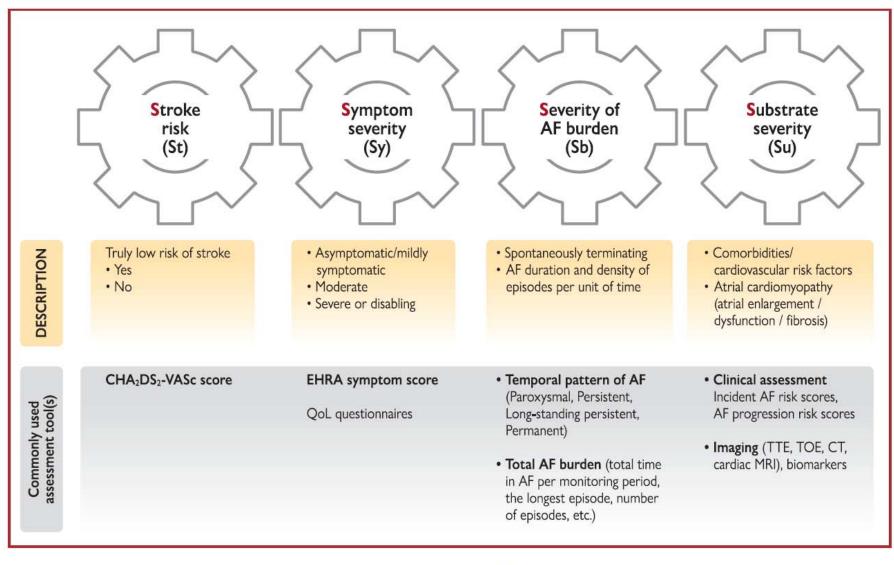
2020 ESC guidelines: Management of AF



Confirm AF and Characterization AF

Recommendations for diagnosis of AF	Class	Level
ECG documentation is required to establish the diagnosis of AF. A standard 12-lead ECG recording or a single-lead ECG tracing of ≥30 s showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical AF.	I	В
Structured characterization of AF, which includes clinical assessment of stroke risk, symptom status, burden of AF, and evaluation of substrate, should be considered in all AF patients, to streamline the assessment of AF patients at different healthcare levels, inform treatment decision making, and facilitate optimal management of AF patients.	lla	С

Characterization AF



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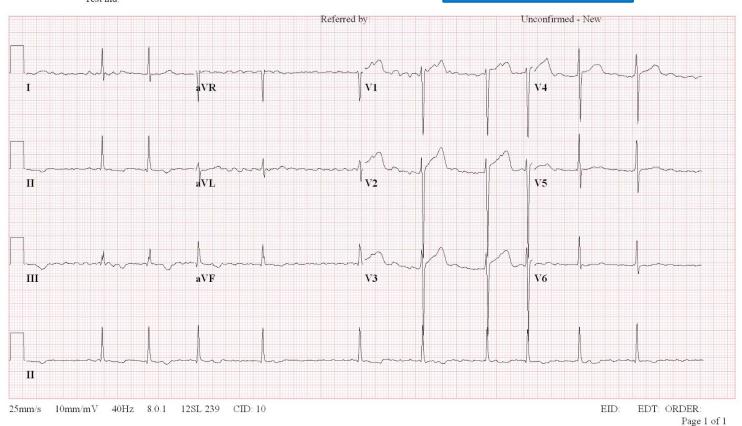
Confirm AF

	Vent. rate	68	BPM
Male	PR interval	a)c	ms
	QRS duration	80	ms
Room:	QT/QTc	370/393	ms
Loc:10	P-R-T axes	* 56	-56

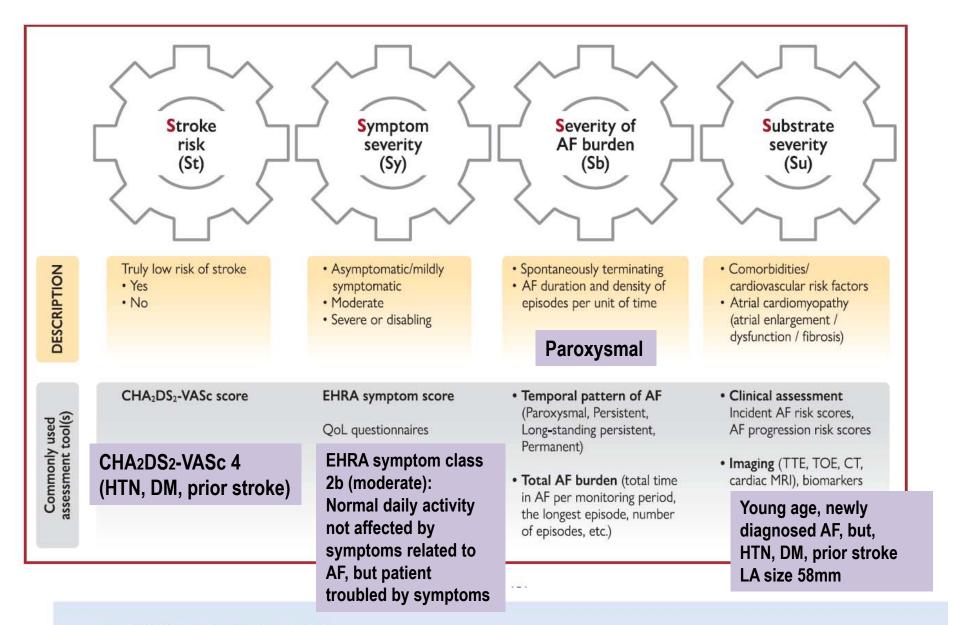
Atrial fibrillation
Moderate voltage criteria for LVH, may be normal variant
T wave abnormality, consider inferior ischemia or digitalis effect
Abnormal ECG

Technician: Test ind:

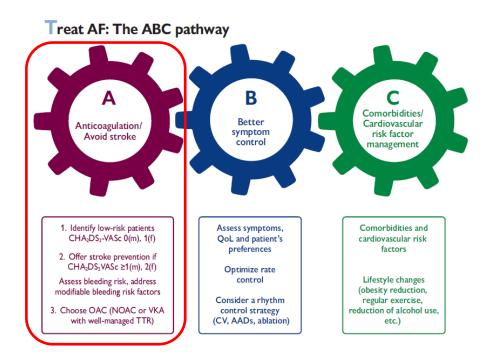
Atrial Fibrillation



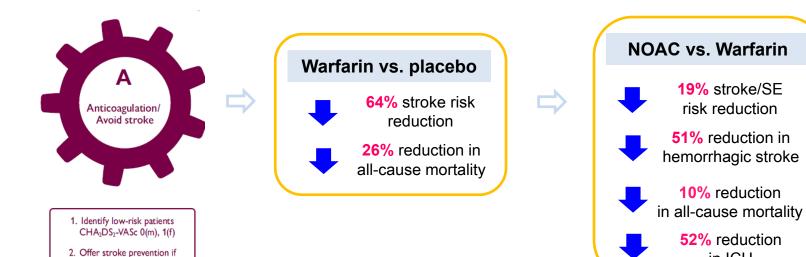
Characterization AF

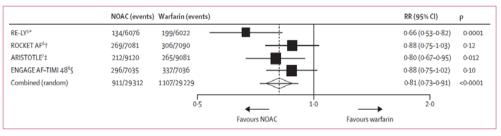


"A": Anticoagulation/Avoid stroke

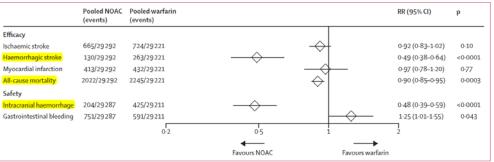


"A": Anticoagulation/Avoid stroke





in ICH



CHA₂DS₂VASc ≥1(m), 2(f) Assess bleeding risk, address modifiable bleeding risk factors

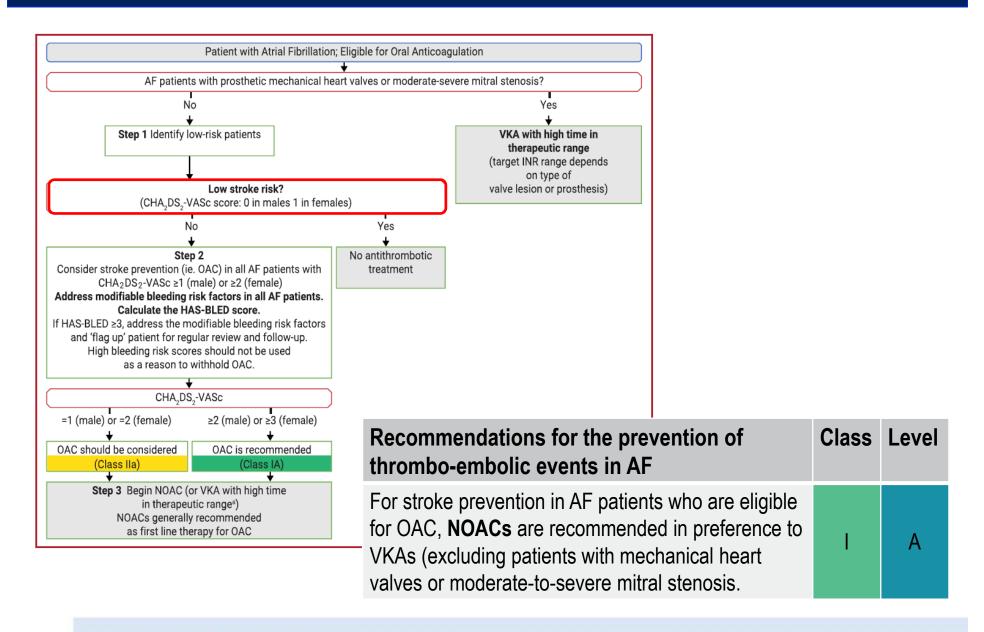
Choose OAC (NOAC or VKA with well-managed TTR)

Current thromboembolic risk stratification in AF patients

CHA2DS2-VASc risk factor	Points
Congestive heart failure Signs/symptoms of HF or objective evidence of reduced LVEF	+1
Hypertension Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	+1
Age 75 years or older	+2
Diabetes mellitus Fasting glucose>125 mg/dL or treatment with oral hypoglycemic agent and/or insulin	+1
Previous stroke, TIA or TE	+2
Vascular disease Previous MI, PAD, or aortic plaque	+1
Age 65-74 years	+1
Sex category (female)	+1

CHA ₂ DS ₂ -VASc	Adjusted stroke rate (%/year)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

2020 ESC AF management guideline

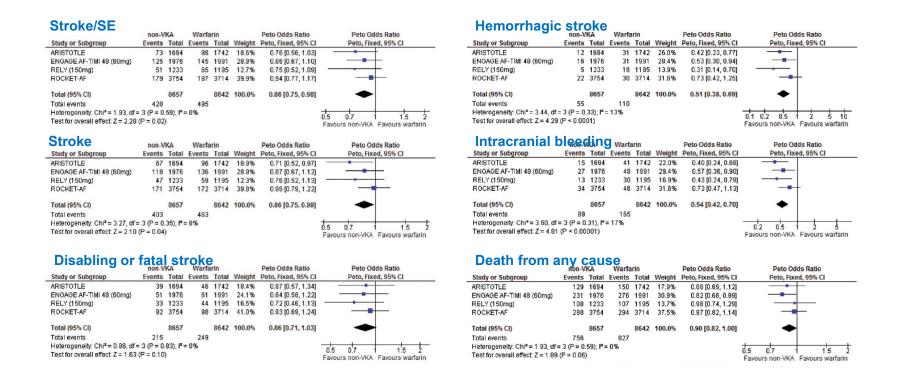


NOAC vs. warfarin in patients with AF and previous stroke or TIA

Table 1. Characteristics of the populations with previous stroke or TIA included in the meta-analysis

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Study population	3623	7468	3436)	5973
Allocated to non-VKA/ warfarin	2428/1195	3754/3714	1694/1742	3982/1991
Period in the therapeutic INR range (for patients allocated to warfarin)	63%	57.1%	65.0%	68.4%
Duration of follow-up (median, IQR)	2.0 (1.14-2.86) years	676 (510–845) days	I.8 (I.4-2.3) years	2.8 years
Males (n, %)	2279 (62.9%)	4538 (60.8%)	2152 (62.6%)	3694 (61.8%)
CHADS2 score				
0-1	0 (0%)	The median	(-,-,	
2	377 (10.4%)	CHADS2 score was 4 (inter-	0.40 (00/)	(67.0%) had a CHADS2 ≤3)
≥3	3246 (89.6%)	quartile range: 3–5)	3168 (92%)	_
Hypertension (n, %)	2783 (76.8%)	6343 (84.9%)	2858 (83%)	5151 (86.2%)
On aspirin at randomization (n, %)	1444 (39.9%)	2808 (37.6%) ^a	1067 (31.1%)	1685 (28.2%)
VKA naive (n, %)	1614 (44.5%)	3039 (40.7%)	1354 (39.4%)	2369 (39.7%)

NOAC vs. warfarin in patients with AF and previous stroke or TIA



This updated meta-analysis in 20,500 AF patients with previous stroke or TIA shows that, compared to warfarin, NOACs are associated with a significant reduction of any stroke or systemic embolism, hemorrhagic stroke, and ICH during a median f/u of 1.8-2.8 years.

NOAC vs. Warfarin in AF patients with a prior history of prior stroke





Article

Effectiveness and Safety of Direct Oral Anticoagulant for Secondary Prevention in Asians with Atrial Fibrillation

Table 2. The cumulative risk of clinical outcomes according to antithrombotic therapy.

Outcome	Warfarin	DOAC	*HR (95% CI)	<i>p</i> -Value	
outcome .	Event (IR)	Event (IR)	_ 111 (35 % C1)		
Recurrent stroke	2294 (4.9)	1184 (4.2)	0.67 (0.62-0.72)	< 0.001	
Major bleeding	1263 (2.6)	633 (2.2)	0.73 (0.66-0.80)	< 0.001	
Composite outcome (Recurrent stroke + major bleeding)	3387 (7.4)	1765 (6.4)	0.69 (0.65-0.73)	< 0.001	
Fatal recurrent stroke	501 (1.0)	307 (1.1)	0.69 (0.59-0.79)	< 0.001	
Fatal major bleeding	188 (0.4)	60 (0.2)	0.50 (0.37-0.68)	< 0.001	
Fatal composite outcome	684 (1.4)	366 (1.3)	0.65 (0.57-0.74)	< 0.001	
All-cause death	3169 (6.4)	2092 (7.4)	0.84 (0.80-0.89)	< 0.001	

^{*} Inverse probability of treatment weighting (IPTW) adjustment. Abbreviation: CI, confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; IR, incidence rate.

Compared to warfarin, **DOACs were associated with lower risk of recurrent stroke (HR 0.67, 95% CI 0.62-0.72)**, major bleeding (HR 0.73, 95% CI 0.65-0.73), and mortality. DOAC use resulted in a consistent trend of improved outcomes in the subgroups of patients with severe, disabling, and recent stroke

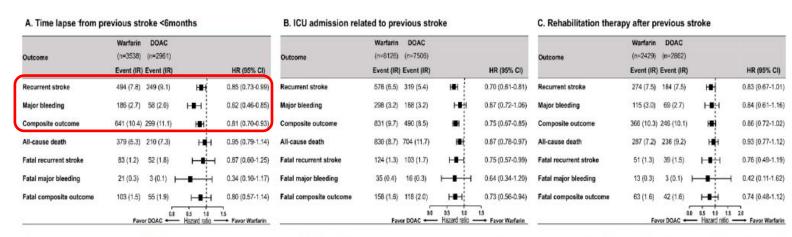
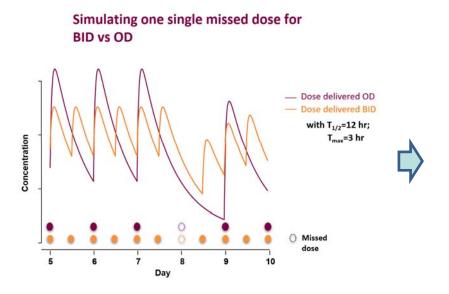
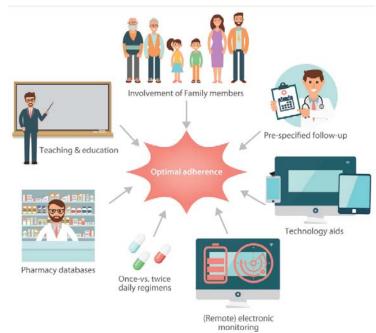


Figure 2. Comparison of clinical outcomes according to antithrombotic therapy among subgroups with recent or severe/disabling stroke. CI = confidence interval, DOAC = direct oral anticoagulant; HR = hazard ratio, ICU = intensive care unit, IR = incidence rate.

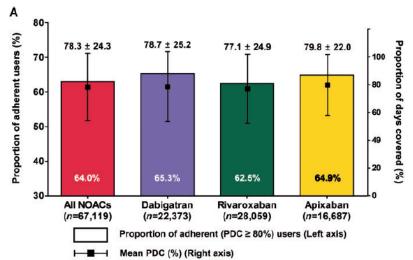
Drug adherence

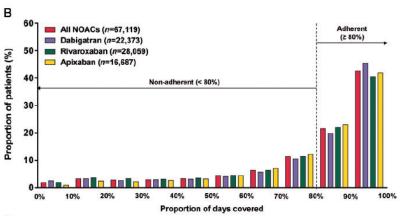
	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Time to peak levels (h)	3	2-4	3	1-2
Half-life (h)	12-17	5-13	9-14	10-14





OAC adherence in Korean AF population





		Major	cardiovascu	lar ev	ent				
	Person- Years	Number of Events	Crude rate (95% CI)					Adjusted HR (95% CI)	P value
Warfarin (reference)	57 395	3525	6.14 (5.94-6.35)			•		1	
NOAC adherent	47 668	2482	5,21 (5.00-5.42)		-			0.71 (0.67-0.76)	<0.001
NOAC non-adherent	25 156	1806	7.18 (6.85-7.52)			<u> </u>		0.94 (0.88-1.01)	0.091
				0.50	0.75	1	1.2	5	
		Ischaemic	stroke/syster	nic e	mbolis	m			
	Person- Years	Number of Events	Crude rate (95% CI)					Adjusted HR (95% CI)	P value
Warfarin (reference)	57 755	2931	5.08 (4.89-5.26)			*		1	-
NOAC adherent	47 853	2013	4.21 (4.03-4.39)	1	•			0.63 (0.60-0.65)	<0.001
NOAC non-adherent	25 377	1483	5 84 (5 55-6 15)			-		0.99 (0.93-1.05)	0.693

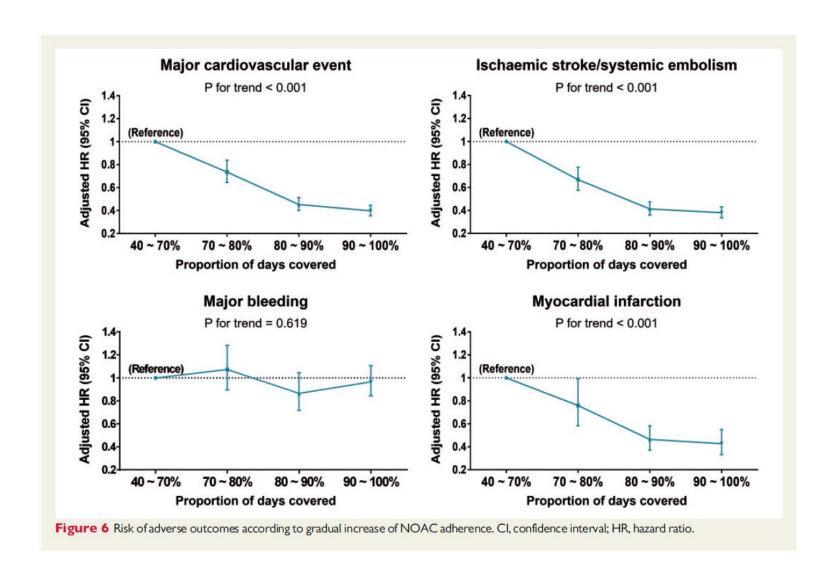
			Major bleedir	ng					
	Person- Years	Number of Events	Crude rate (95% CI)					Adjusted HR (95% CI)	P value
Warfarin (reference)	58 755	1888	3.21 (3.07-3.36)			•		1	
NOAC adherent	48 140	1263	2.62 (2.48-2.77)		-			0.77 (0.71-0.83)	<0.001
NOAC non-adherent	25 298	696	2.75 (2.55-2.96)		-	1		0.79 (0.73-0.87)	<0.001
				0.50	0.75	1	1.2	5	

0.50 0.75

1.25

		My	ocardial infarctio	n				
	Person- Years	Number of Events	Crude rate (95% CI)				Adjusted HR (95% CI)	P value
Warfarin (reference)	60 582	885	1.46 (1.37-1.56)		•		1	141
NOAC adherent	48 569	569	1.17 (1.08-1.27)	-	-		0.90 (0.80-1.00)	0.072
NOAC non-adherent	26 141	443	1.69 (1.54-1.86)		-	-	1.13 (1.03-1.25)	0.014
			0.50	0.75	1	1.2	5	

Better adherence, better clinical outcomes



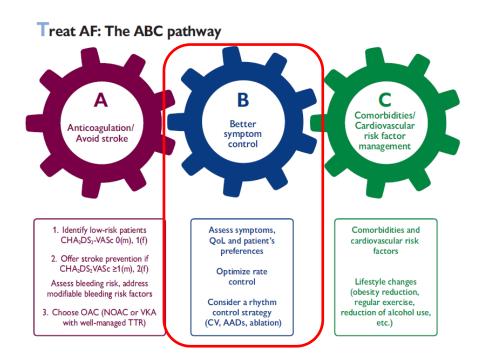
CHA2DS2-VASc 4, Start NOAC

Summary

- Left PCA territory infarction
- Sx: Rt. Hemianopsia
- Risk factor: HTN, DL, obesity, exsmoker, newly documented AF
- Mechanism: CE
- Med: ASA->DAPT->NOAC
- Initial NIHSS 1

Medication

- Rivaroxaban 20mg 1T daily
- Atorvastatin 20mg 1T daily
- Famotidine 20mg 1T daily
- Amlodipine 5mg 1T bid
- Valsartan 80mg 1T daily
- Fenofibrate 160mg 1T daily
- Ursa 100mg 1T tid
- Finasteride 5mg 1T daily
- Tamsulosine 0.2mg 1T daily





Assess symptoms, QoL and patient's preferences

Optimize rate control

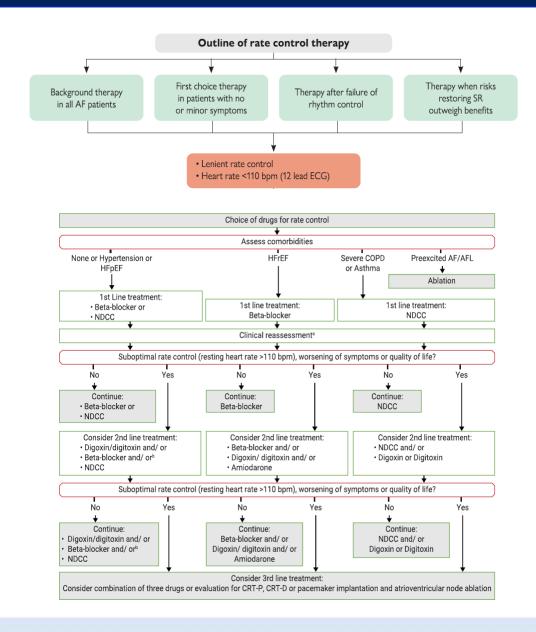
Consider a rhythm control strategy (CV, AADs, ablation)



Assess symptoms, QoL and patient's preferences

Optimize rate control

Consider a rhythm control strategy (CV, AADs, ablation)



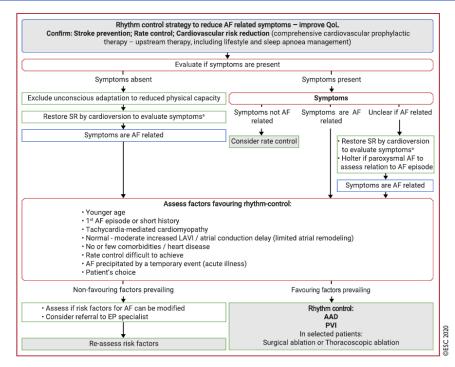


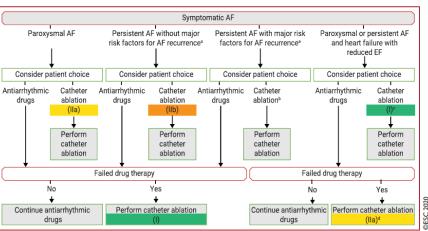
Assess symptoms, QoL and patient's preferences

Optimize rate control

Consider a rhythm control strategy (CV, AADs, ablation)

Recommendations for rhythm control	Class	Level
Rhythm control therapy is recommended for symptom and QoL improvement in symptomatic patients with AF	ı	А





Association of burden of AF with risk of ischemic stroke

JAMA Cardiology | Original Investigation

Association of Burden of Atrial Fibrillation With Risk of Ischemic Stroke in Adults With Paroxysmal Atrial Fibrillation The KP-RHYTHM Study

Alan S. Go, MD; Kristi Reynolds, PhD, MPH; Jingrong Yang, MA; Nigel Gupta, MD; Judith Lenane, RN, MHA; Sue Hee Sung, MPH; Teresa N. Harrison, SM; Taylor I. Liu, MD, PhD; Matthew D. Solomon, MD, PhD

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study conducted from October 2011 and October 2016 at 2 large integrated health care delivery systems used an extended continuous cardiac monitoring system to identify adults who were found to have paroxysmal atrial fibrillation on 14-day continuous ambulatory electrocardiographic monitoring.

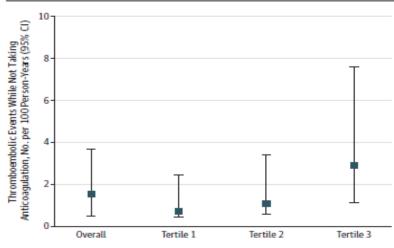
EXPOSURES The burden of atrial fibrillation was defined as the percentage of analyzable wear time in atrial fibrillation or flutter during the up to 14-day monitoring period.

MAIN OUTCOMES AND MEASURES Ischemic stroke and other arterial thromboembolic events occurring while patients were not taking anticoagulation were identified through November 2016 using electronic medical records and were validated by manual review. We evaluated the association of the burden of atrial fibrillation with thromboembolism while not taking anticoagulation after adjusting for the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) or CHA2DS2-VASc stroke risk scores.

RESULTS Among 1965 adults with paroxysmal atrial fibrillation, the mean (SD) age was 69 (11.8) years, 880 (45%) were women, 496 (25%) were persons of color, the median ATRIA stroke risk score was 4 (interquartile range [IQR], 2-7), and the median CHA2DS2-VASc score was 3 (IOR, 1-4). The median burden of atrial fibrillation was 4.4% (IOR, 1.1%-17.23%). Patients with a higher burden of atrial fibrillation were less likely to be women or of Hispanic ethnicity, but had more prior cardioversion attempts compared with those who had a lower burden. After adjusting for either ATRIA or CHA2DS2-VASc stroke risk scores, the highest tertile of atrial fibrillation burden (≥11.4%) was associated with a more than 3-fold higher adjusted rate of thromboembolism while not taking anticoagulants (adjusted hazard ratios, 3.13 [95% CI, 1.50-6.56] and 3.16 [95% CI, 1.51-6.62], respectively) compared with the combined lower 2 tertiles of atrial fibrillation burden. Results were consistent across demographic and clinical subgroups.

CONCLUSIONS AND RELEVANCE A greater burden of atrial fibrillation is associated with a higher risk of ischemic stroke independent of known stroke risk factors in adults with paroxysmal atrial fibrillation.

Figure 3. Thromboembolic Event Rates While Not Taking Anticoagulation, Overall and Stratified by Atrial Fibrillation (AF) Burden Tertile in 1965 Adults With Confirmed Paroxysmal AF

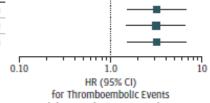


Overall and Stratified by Tertile of Percentage of Time in Atrial Fibrillation or Atrial Flutter

A Cumulative burden and duration of longest episode of AF

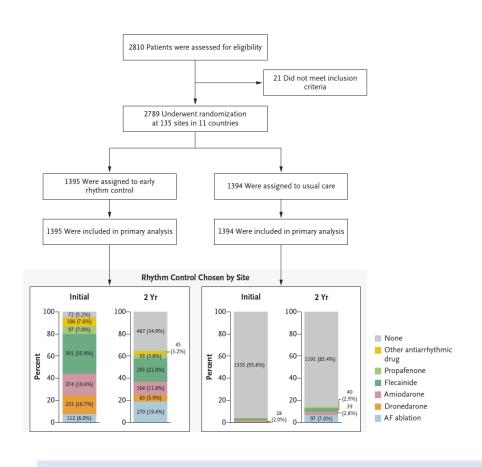
Cumulative burden of AF (%) (third tertile vs combined first and second tertile)

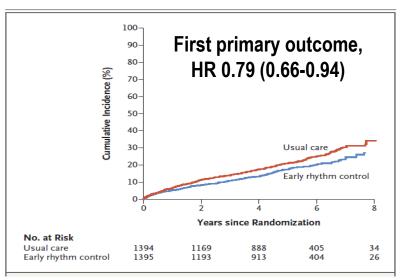
1965	HR (95% CI)
UnadJusted	3.15 (1.51-6.61)
Adjusted for ATRIA stroke risk score	3.13 (1.50-6.56)
Adjusted for CHA ₂ DS ₂ -VASc	3.16 (1.51-6.62)



Early rhythm control reduced the risk of stroke

Study design: Randomly assigned patients who had early AF (diagnosed ≤1 year before enrollment) and cardiovascular conditions to receive either **early rhythm control or usual care Primary endpoint:** composite of death from cardiovascular causes, stroke, or hospitalization with worsening heart failure or acute coronary syndrome





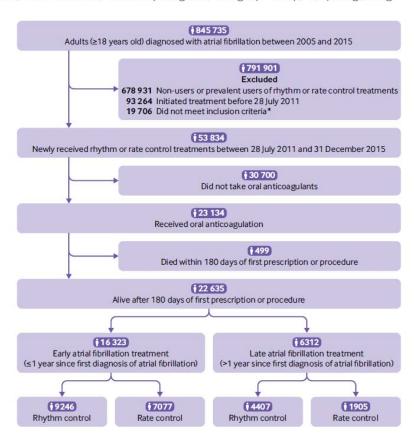
Component of primary outcome	HR (95% CI)
Death from cardiovascular cause	0.72 (0.52-0.98)
Stroke	0.65 (0.44-0.97)
Hospitalization for worsening of HF	0.81 (0.65-1.02)
Hospitalization for ACS	0.83 (0.58-1.19)

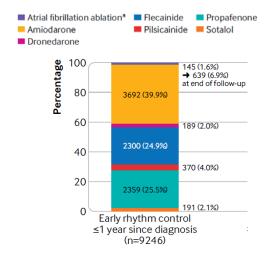
Early rhythm control reduced the risk of stroke

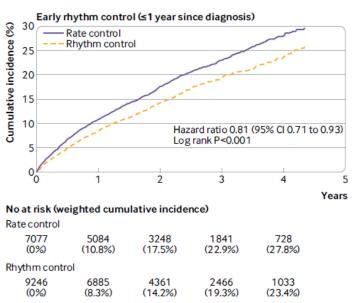
RESEARCH

Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation: nationwide cohort study

Daehoon Kim, ¹ Pil-Sung Yang, ² Seng Chan You, ³ Jung-Hoon Sung, ² Eunsun Jang, ¹ Hee Tae Yu, ¹ Tae-Hoon Kim, ¹ Hui-Nam Pak, ¹ Moon-Hyoung Lee, ¹ Gregory Y H Lip, ⁴ Boyoung Joung ¹



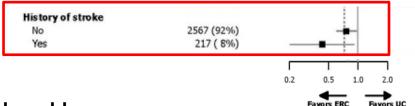




Benefit of early rhythm control in patients with prior stroke

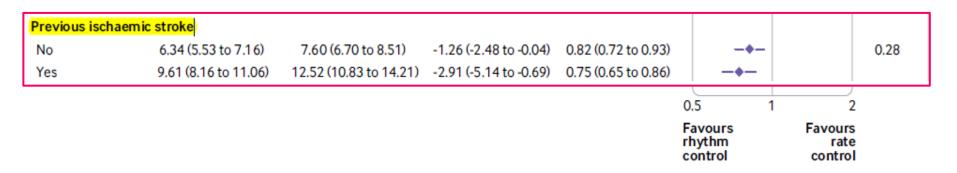
EAST-AFNET

Previous stroke or TIA: Early rhythm control n=175 (12.5%) vs. Usual care n=153 (11.0%)



EAST-AFNET Korean real-world

Previous ischemic stroke: Early rhythm control n=2841 (30.7%) vs. rate control n=2400 (33.9%)

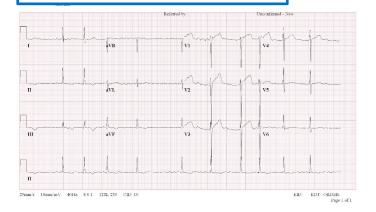


N=120,512 (prior stroke, incident AF) from Korean nationwide population-based cohort

Clinical outcome (early rhythm control vs. usual care)	aHR (95% CI)
Stroke	0.833 (0.783-0.886)
Death	0.930 (0.901-0.969)

ECG and Holter

Atrial Fibrillation



No AF/AFL

General

88086 QRS complexes

2979 Ventricular beats (3%)

297 Supraventricular beats (< 1%)

< 1 % of total time classified as noise

Heart Rates

49 Minimum at 00:01:48 21-May

64 Average

116 Maximum at 07:44:32 21-May

5 Beats in tachycardia (>=100 bpm), < 1% total
32116 Beats in bradycardia (<=60 bpm), 36% total
1.68 Seconds Max R-R at 23:46:43 20-May

Supraventriculars (S, J, A)

261 Isolated

8 Couplets

Bigeminal cycles

4 Runs totaling 20 beats

8 Beats longest run 109 bpm 08:35:06 21-May 3 Beats fastest run 118 bpm 17:34:24 20-May

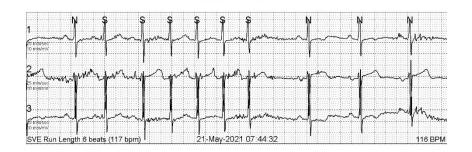
Ventriculars (V, F, E, I)

2867 Isolated

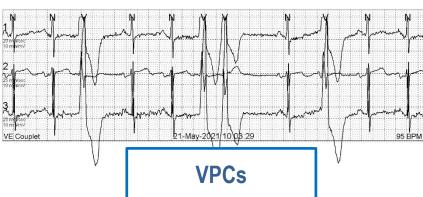
56 Couplets

0 Bigeminal cycles

0 Runs totaling 0 beats



Short run PAT



Cardiology consultation:

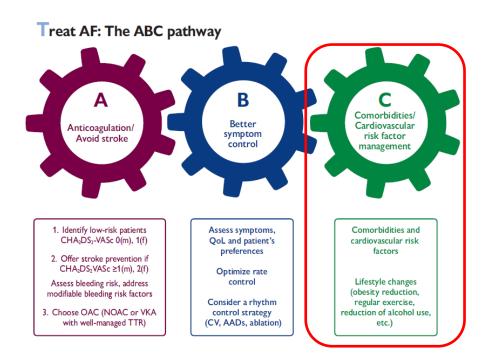
안녕하십니까 교수님

상기 환자 Lt. PCAt infarction with newly documented A.fib으로 본과 입원하고 있습니다. 내원 당시 NSR에 frequent APC, VPC 있었으나 stroke unit 에서 continuous monitoring 시 확인하였을 때 5/16 오후부터 AF with A.flutter 로 리듬 변하여 5/17 monitoring off 할 때까지지속되었습니다. HTN, DL, obesity 의 risk factor 있던 환자입니다.

Echocardiography 결과 EF 56%, No RWMA이며 LAVI 59.3 mL/m2 으로 LA가 확장되어 있습니다. Rate는 50-80회 /분으로 현재 rate control 필요성은 없을 것으로 생각되며, 금-토 holter 이후 퇴원 예정으로 A.fib burden 확인할 예정입니다. 환자 나이 아직 고령은 아니고 A.fib 이 paroxysmal 하게 발생한 것이라면 rhythm control 의 candidate가 될 수도 있으리라 사료됩니다. Holter 결과는 퇴원 이후 확인할 예정으로 신경과 및 귀과외래 함께 f/u 해도 될지 여쭙습니다. 바쁘신 와중 대단히 감사합니다.

NR R2 000 배상

"C", Comorbidities/Cardiovascular risk factor management



Stroke risk factors in patients with AF

CHA2DS2-VASc score

Most commonly studied clinical risk factors (a systematic review) ³²⁴	Positive studies/All studies	Other clinical risk factors ³²⁵	Imaging biomarkers ^{291,326–328}	Blood/urine biomarkers ³²⁹⁻³³²
Stroke/TIA/systemic embolism	15/16	Impaired renal function/ CKD	Echocardiography	Cardiac troponin T and I Natriuretic peptides
Hypertension	11/20	OSA	LA dilatation	Cystatin C
Ageing (per decade)	9/13	HCM	Spontaneous contrast or	Proteinuria
Structural heart disease	9/13	Amyloidosis in degenerative cerebral and heart diseases	thrombus in LA Low LAA velocities	CrCl/eGFR CRP
Diabetes mellitus	9/14	Hyperlipidaemia	Complex aortic plaque	IL-6
Vascular disease	6/17	Smoking	Cerebral imaging	GDF-15 von Willebrand factor
CHF/LV dysfunction	7/18	Metabolic syndrome ³³³	Small-vessel disease	D-dimer
Sex category (female)	8/22	Malignancy		D-diffe

CHF = congestive heart failure; CKD = chronic kidney disease; CrCl = creatinine clearance; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; GDF-15 = growth differentiation factor-15; IL-6 = interleukin 6; LA = left atrium; LAA = left atrial appendage; LV = left ventricular; OSA = obstructive sleep apnoea; TIA = transient ischaemic attack.

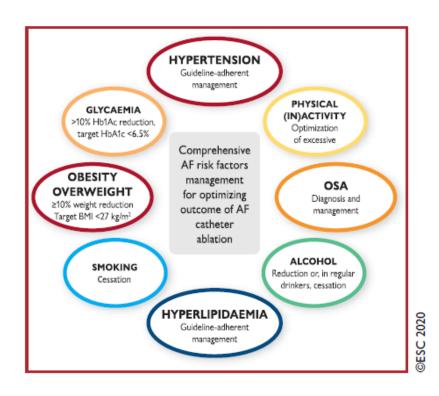
Modifiable risk factor?

Non-modifiable

Modifiable

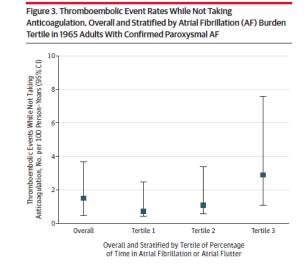
Most commonly studied clinical risk factors (a systematic review) ³²⁴	Positive studies/All studies	Other clinical risk factors ³²⁵
Stroke/TIA/systemic embolism	15/16	Impaired renal function/
		CKD
Hypertension	11/20	OSA
Ageing (per decade)	9/13	HCM
Structural heart disease	9/13	Amyloidosis in degenerative
		cerebral and heart diseases
Diabetes mellitus	9/14	Hyperlipidaemia
Vascular disease	6/17	Smoking
CHF/LV dysfunction	7/18	Metabolic syndrome ³³³
Sex category (female)	8/22	Malignancy

Risk factors for AF contributing to the development of an abnormal substrate



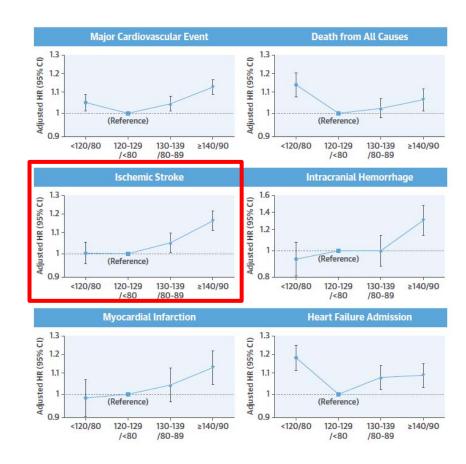
JAMA Cardiology | Original Investigation

Association of Burden of Atrial Fibrillation With Risk of Ischemic Stroke in Adults With Paroxysmal Atrial Fibrillation The KP-RHYTHM Study

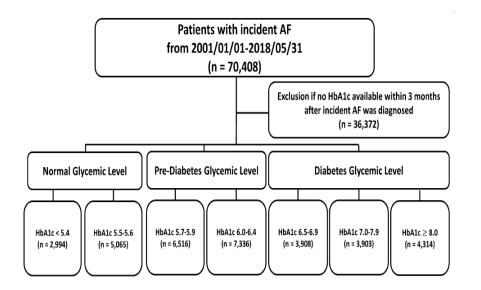


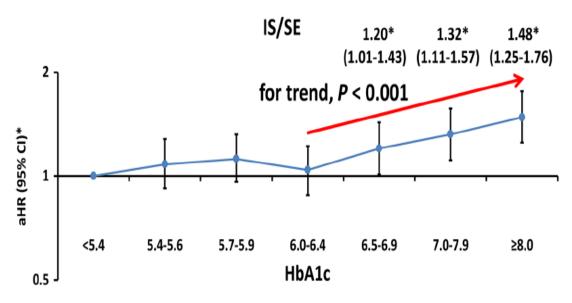
BP control status and outcome in AF patients

298,374 Korean adults with OAC-naïve, AF obtained from the KHIS database from 2005 to 2015



Glycemic status and the risks of thromboembolism in AF patients





Statin therapy in acute cardioembolic stroke with no guidance-based indication

ARTICLE

Statin therapy in acute cardioembolic stroke with no guidance-based indication

Objective

It is uncertain whether patients with cardioembolic stroke and without a guidance-based indication for statin therapy should be administered a statin for prevention of subsequent vascular events. This study was performed to determine whether the statin therapy is beneficial in preventing major vascular events in this population.

Methods

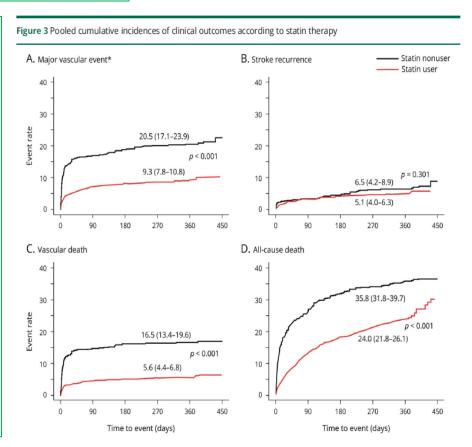
Using a prospective multicenter stroke registry database, we identified patients with acute cardioembolic stroke who were hospitalized between 2008 and 2015. Patients who had other established indications for statin therapy according to current guidelines were excluded. Major vascular event was defined as a composite of stroke recurrence, myocardial infarction, and vascular death. We performed frailty model analysis with the robust sandwich variance estimator using the stabilized inverse probability of treatment weighting method to estimate hazard ratios of statin therapy on outcomes.

Results

Of 6,124 patients with cardioembolic stroke, 2,888 (male 44.6%, mean age 75.3 years, 95% confidence interval [CI] 74.8–75.8) were eligible, and 1,863 (64.5%) were on statin therapy during hospitalization. After a median follow-up of 359 days, cumulative incidences of major vascular events were 9.3% in the statin users and 20.5% in the nonusers (p < 0.001 by log-rank test). The adjusted hazard ratios of statin therapy were 0.39 (95% CI 0.31–0.48) for major vascular events, 0.81 (95% CI 0.57–1.16) for stroke recurrence, 0.28 (95% CI 0.21–0.36) for vascular death, and 0.53 (95% CI 0.45–0.61) for all-cause death.

Conclusion

Starting statin during the acute stage of ischemic stroke may reduce the risk of major vascular events, vascular death, and all-cause death in patients with cardioembolic stroke with no guidance-based indication for statin.



Major vascular event: stroke recurrence, MI, and vascular death

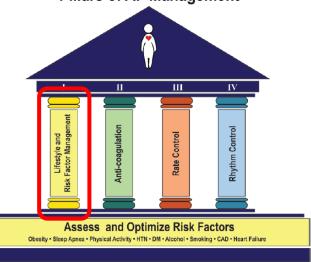
Lifestyle behavior

Updated ESC AF guideline



Comorbidities and cardiovascular risk factors

Lifestyle changes (obesity reduction, regular exercise, reduction of alcohol use, etc.) **Pillars of AF Management**



In addition to the traditional 3 strategies of AF management, a fourth approach addressing lifestyle and risk factors is suggested.

You are diagnosed with AF. You have higher stroke risk than non-AF population. I will prescribe OAC and antiarrhythmic drugs...blah blah, if still symptomatic after AAD, we can consider AF RFCA... blah blah blah

Is there anything else I should be careful about? Food? Coffee? Alcohol? Smoking??...



Smoking is a risk factor for stroke in AF patients

Identifying Patients at High Risk for Stroke Despite Anticoagulation

A Comparison of Contemporary Stroke Risk Stratification Schemes in an Anticoagulated Atrial Fibrillation Cohort

Gregory Y.H. Lip, MD; Lars Frison, PhD; Jonathan L. Halperin, MD; Deirdre A. Lane, PhD

Background and Purpose—The risk of stroke in patients with atrial fibrillation (AF) is not homogeneous, and various clinical risk factors have informed the development of stroke risk stratification schemes (RSS). Among anticoagulated cohorts, the emphasis should be on the identification of patients who remain at high risk for stroke despite anticoagulation.

Methods—We investigated predictors of thromboembolism (TE) risk in an anticoagulated AF clinical trial cohort (n=7329 subjects) and tested the predictive value of contemporary RSS in this cohort: CHADS₂, Framingham, NICE 2006, American College of Cardiology/American Heart Association/European Society of Cardiology 2006, the 8th American College of Chest Physicians guidelines and the CHA₂DS₂-VASc schemes.

Results—On multivariate analysis, significant predictors of TE were stroke/TIA (hazard ratio [HR], 2.24; P<0.001), age 75 years or older (HR, 1.77; P=0.0002), coronary artery disease (HR, 1.52; P=0.0047), and smoking (HR, 2.10; P=0.0005), whereas reported alcohol use (HR, 0.70; P=0.02) was protective. Comparison of contemporary RSS demonstrated variable classification of AF patients into risk strata, although c-statistics for TE were broadly similar among the RSS tested and varied between 0.575 (NICE 2006) and 0.647 (CHA₂DS₂-VASc). CHA₂DS₂-VASc classified 94.2% as being at high risk, whereas most other RSS categorized two-thirds as being at high risk. Of the 184 TE events, 181 (98.4%) occurred in patients identified as being at high risk by the CHA₂DS₂-VASc schema. There was a stepwise increase in TE with increasing CHA₂DS₂-VASc score (P_{trend}<0.0001), which had the highest HR (3.75) among the tested schemes. The negative predictive value (ie, the percent categorized as "not high risk" actually being free from TE) for CHA₂DS₂-VASc was 99.5%.

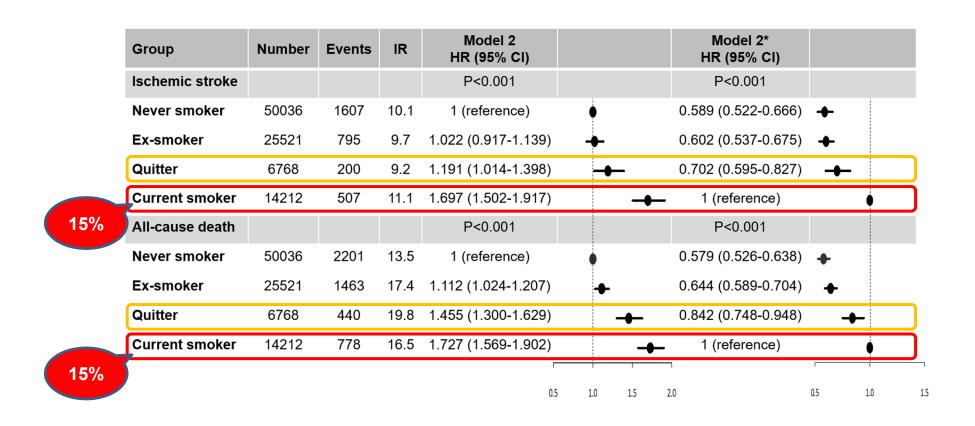
Conclusion—Coronary artery disease and smoking are additional risk factors for TE in anticoagulated AF patients, whereas alcohol use appears protective. Of the contemporary stroke RSS, the CHA₂DS₂-VASc scheme correctly identified the greatest proportion of AF patients at high risk, despite the similar predictive ability of most RSS evidenced by the c-statistic. (Stroke. 2010;41:2731-2738.)

Key Words: atrial fibrillation warfarin

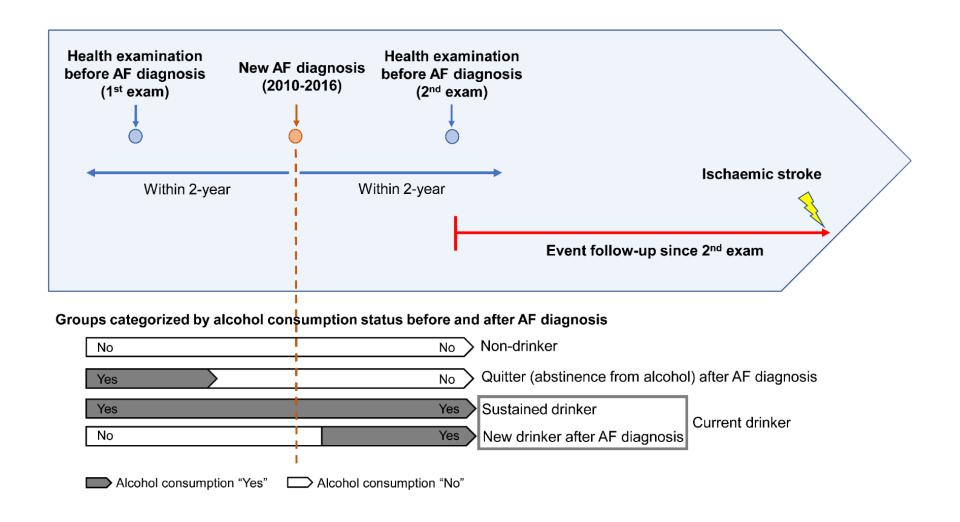
Table 2.	Univariate and Multivariate	Predictive Power	of Risk Factors for	Thromboembolic Events

	per Patie Risk I	Rate (% ent-Year) Factor sent	Univariate Analys	ses	Multivariate Analy	ses*
Risk Factor	Yes	No	Hazard Ratio† (95% CI)	P Value	Hazard Ratio+ (95% CI)	P Value
Stroke/TIA	3.05	1.28	2.35 (1.74, 3.17)	< 0.0001	2.24 (1.66, 3.02)	< 0.0001
Age≥75 years	2.25	1.26	1.78 (1.34, 2.38)	< 0.0001	1.77 (1.32, 2.38)	0.0002
Coronary artery disease	2.04	1.31	1.57 (1.17, 2.10)	0.0025	1.52 (1.14, 2.04)	0.0047
Smoking	2.68	1.54	1.75 (1.16, 2.63)	0.0074	2.10 (1.38, 3.18)	0.0005
Alcohol	1.31	1.91	0.69 (0.51, 0.93)	0.014	0.70 (0.52, 0.95)	0.020
Systemic embolic event	3.24	1.56	2.08 (1.24, 3.47)	0.0052		
Female	2.08	1.44	1.44 (1.07, 1.93)	0.016		
Diabetes mellitus	1.92	1.55	1.23 (0.89, 1.71)	0.21		
Hypertension	1.72	1.38	1.24 (0.86, 1.79)	0.24		
Left ventricular dysfunction	1.67	1.62	1.03 (0.77, 1.39)	0.84		

Quitters was associated with lower risks of ischemic stroke and death compared to current smokers.

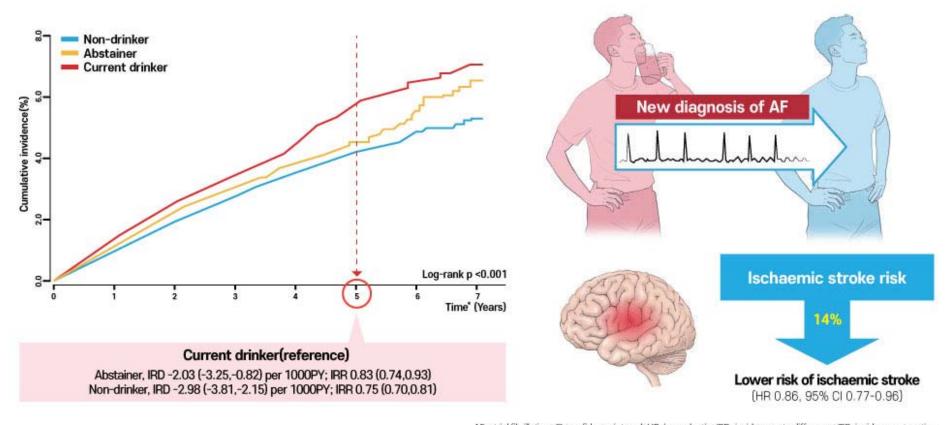


The benefit of alcohol abstinence on the risk of ischemic stroke in AF patients



Alcohol abstinence was associated with a lower risk of ischemic stroke

Weighted cumulative incidence curve of ischaemic stroke according to drinking status before and after AF diagnosis Abstinence from alcohol after new diagnosis of AF and the risk of ischemic stroke

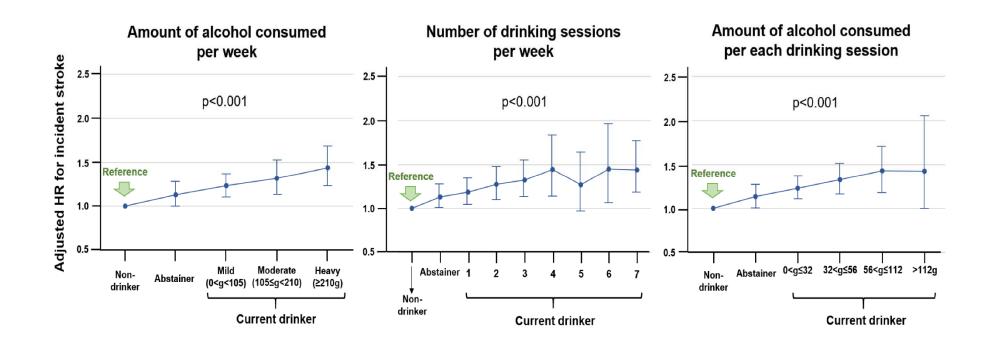


AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; IRD, incidence rate difference; IRR, incidence rate ratio.

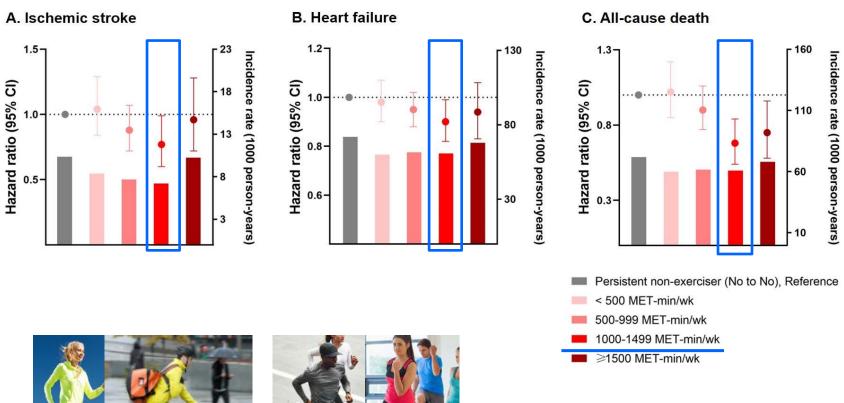
Dose-response relationship

Amongst current drinkers, a greater amount of alcohol consumption per week was associated with a higher risk of ischemic stroke.

Both frequent drinking and binge drinking per each drinking session were significant risk factors for incident ischemic stroke.



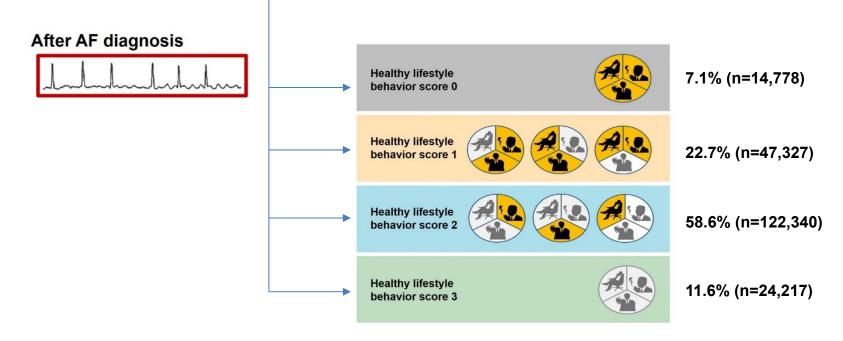
Regular exercise and the risk of stroke, heart failure, death in AF patients



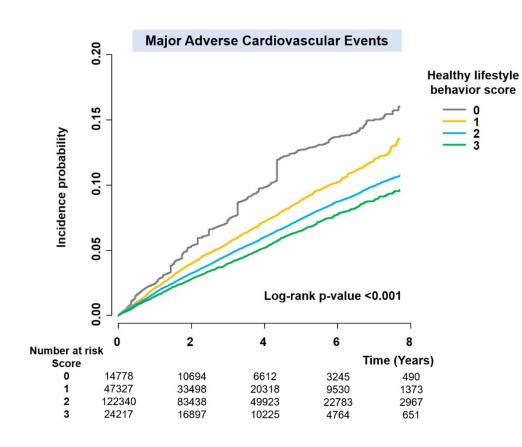
Vigorous, 140-210 min/week

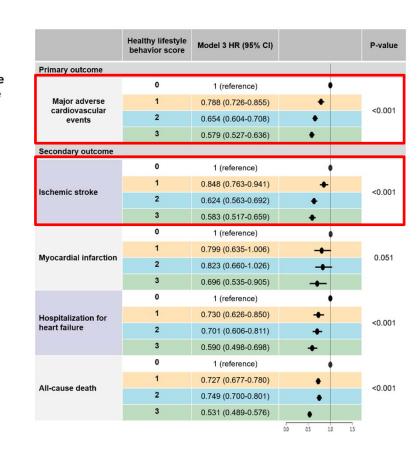
Healthy lifestyle combination and the risk of MACE in AF patients

Patients with **new-onset AF** between January 1, 2009 and December 31, 2016 who underwent national health screening examination within 2-year after their AF diagnosis (n=208,662)



Healthy lifestyle combination and the risk of MACE in AF patients





Prior ischemic stroke (n=53,559, 25%)

MACE	Number	aHR (95% CI)
HLS 0	2080	1 (reference)
HLS 1	9065	0.764 (0.696-0.838)
HLS 2	35,868	0.643 (0.588-0.703)
HLS 3	6546	0.558 (0.502-0.622)

Recommendations for lifestyle interventions and management of risk factors and concomitant diseases in patients with AF

Recommendations	Class	Level
Identification and management of risk factors and concomitant disease is recommended as an integral part of treatment in AF patients		В
Modification of unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity.		В
Attention to good BP control is recommended in AF patients with hypertension to reduce AF recurrences and risk of stroke and bleeding.		В
Advice and management to avoid alcohol excess should be considered for AF prevention and in AF patients considered for OAC therapy.	lla	В
Physical activity should be considered to help prevent AF incidence or recurrence, with the exception of excessive endurance exercise, which may promote AF.	lla	С

Proactive "C"

```
Height: 169 cm / Weight: 92.8 kg / BMI: 32.49 kg/m<sup>2</sup>

Medical History>
# HTN on aspirin
# DM not on med
# Dyslipidemia
# BPH
```

Ex-smoker, 60 PY (quit 10YA) Current drinker, 소주 2병/주 Exercise?? 157/98 - 60 - 18 - 36.7

BP fluctuation : maximum 174/98 - 58 - 18 - 36.9

Fasting glucose 126~131 HbA1c 5.9

Total cholesterol 216 / TG 61 / HDL 60 / LDL 153 BUN/Cr 20/0.94

Adding 'B' and 'C' on 'A' can bring greater risk reduction for stroke.

Warfarin vs. placebo



64% stroke risk reduction



26% reduction in all-cause mortality

NOAC vs. Warfarin



19% stroke/SE risk reduction



51% reduction in hemorrhagic stroke



10% reduction in all-cause mortality



52% reduction in ICH



- 1. Identify low-risk patients CHA₂DS₂-VASc 0(m), 1(f)
- 2. Offer stroke prevention if CHA₂DS₂VASc ≥1(m), 2(f)

Assess bleeding risk, address modifiable bleeding risk factors

Choose OAC (NOAC or VKA with well-managed TTR)

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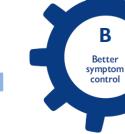
52% reduction in ICH



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- 2. Offer stroke prevention if CHA₂DS₂VASc ≥1(m), 2(f)

Assess bleeding risk, address modifiable bleeding risk factors

3. Choose OAC (NOAC or VKA with well-managed TTR)



Assess symptoms, QoL and patient's preferences

Optimize rate control

Consider a rhythm control strategy (CV, AADs, ablation)





Comorbidities and cardiovascular risk factors

Lifestyle changes (obesity reduction, regular exercise, reduction of alcohol use, etc.)

