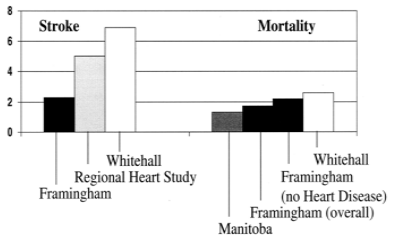
소강당

심방세동과 최신 항응고요법

남 기 병
서울아산병원 내과

Clinical Impact of Atrial Fibrillation

QoL
Hospitalization
Stroke
CHF
Mortality



JACC Vol. 38, No. 4, 2001

항응고치료는 왜 중요한가?

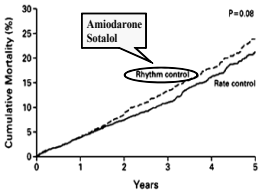
Rhythm control

Rate control

Anticoagulation

AFFIRM

4060 enrolled patients from 213 sites in the US, Canada
Age: >65 y.o. (69.7±9.0 years)
Risk factors for stroke
AF lasting > 6 hours, episode lasted at least 2 days (70%)
Mean follow up time: 3.5 years (maximum, 6 yrs)



No. of Deaths	number (percent)				
Rhythm control	0	80 (4)	175 (9)	257 (13)	314 (18)	352 (24)
Rate control	0	78 (4)	148 (7)	210 (11)	275 (16)	306 (21)

~~사망율~~
~~심부전~~
~~뇌경색~~
~~병원입원~~
~~삶의 질~~
~~증상개선~~

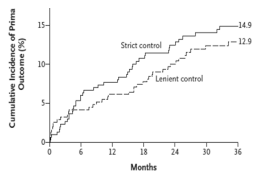
운동능력

RACE II

ORIGINAL ARTICLE

Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

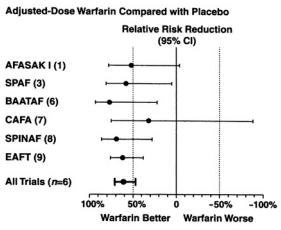
Isabelle C. Van Gelder, M.D., Hessel F. Groenveld, M.D., Harry J.G.M. Crijns, M.D., Ype S. Tuininga, M.D., Jan G.P. Tijssen, Ph.D., A. Marco Alings, M.D., Hans L. Hillege, M.D., Johanna A. Bergsma-Kadijk, M.Sc., Jan H. Cornel, M.D., Otto Kamp, M.D., Raymond Tukkie, M.D., Hans A. Bosker, M.D., Dirk J. Van Veldhuisen, M.D., and Maarten P. Van den Berg, M.D., for the RACE II Investigators*



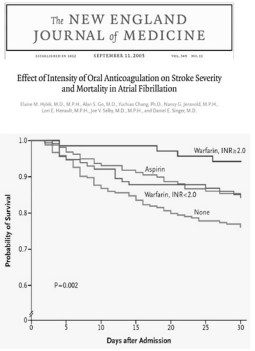
No. at Risk							
Strict control	303	282	273	262	246	212	131
Lenient control	311	298	290	285	255	218	138

~~사망율~~
~~심부전~~
~~뇌경색~~
~~병원입원~~
~~증상개선~~

항응고치료의 효과



Ann Intern Med 1999;131:492-501



N Engl J Med 2003;349:1019-26.

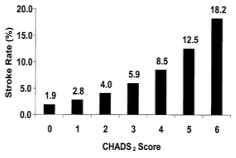
뇌졸중의 빈도는?
항응고치료의 대상은?

Anticoagulation 필요성 여부 (항응고 치료)

판막치환수술, 승모판막질환: 17%/년
비판막질환: Risk factors (CHADS2)
Peri-cardioversioin

Table 3. $CHADS_2$ Risk Stratification Scheme (14)

Risk Factors	Score
C Recent congestive heart failure	1
H Hypertension	1
A Age ≥75 yrs	1
D Diabetes mellitus	1
S_2 History of stroke or transient ischemic attack	2



(J Am Coll Cardiol 2004;43:929 –35)

Warfarin : relative risk reduction, 68%
Annual rate of stroke: from 4.5% to 1.4%/yr
Major hemorrhagic complication: 1.0 to 1.3%/yr
cf. Asprin: relative risk reduction, 33%

CHA_2DS_2-VASc score

$CHADS_2$

Risk Factor	Score
Congestive heart failure	1
Hypertension	1
Age ≥75y	1
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Maximum score	6

CHA_2DS_2-VASc

Risk Factor	Score
Congestive heart failure	1
Hypertension	1
Age ≥75y	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease	1
Age 65-74y	1
Female	1
Maximum score	9

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	Patients (n=7329)	Adjusted stroke rate (%/year)[c]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

*** Vascular ds :**
Prior myocardial infarction, peripheral artery disease, aortic plaque

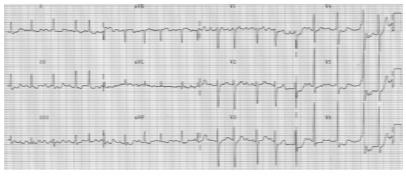
European Heart Journal 2010, 31:2369
Canadian Journal of Cardiology 27 (2011) 7-13

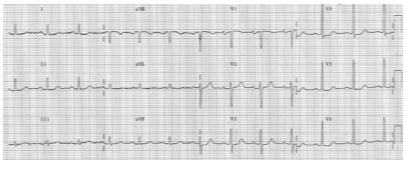
심방세동의 type에 따른 뇌졸중 위험은?

지속성 심방세동

발작성 심방세동

증례 F/75
고혈압으로 약물치료 중이던 75세 여자 환자가 발작성 심계항진으로 응급실 방문하였다.
당뇨로 10년간 경구혈당강하제 복용 중.매년 정기 신검에서 찍은 심전도는 정상.
심계항진이 1달에 1-2차례 있었으나 증상이 견딜 만 하여 심전도를 찍은 적은 없었음.
심한 증상은 1년에 1-2번. 응급실 도착 후 2시간 후 자발적으로 정상 동율동으로 전환.





Stroke in Paroxysmal AF

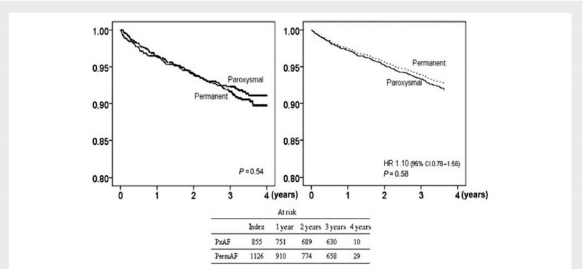


Figure 1 Survival free from ischaemic stroke (163) in paroxysmal atrial fibrillation (AF) and permanent AF. Unadjusted incidence to the left, multivariably adjusted to the right. Note abbreviation of scale

European Heart Journal (2010) 31, 967–975

Stroke in Paroxysmal AF

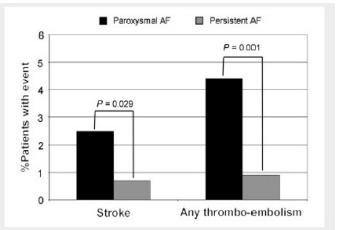


Figure 4 Thrombo-embolic complications during 1 year after baseline cardioversion in paroxysmal and persistent atrial fibrillation.

Nieuwlaat et al. *Eur Heart J. 2008;29(7):915-922.*

항응고 치료의 대상

판막치환수술, 승모판막질환: prosthetic valve, mitral stenosis

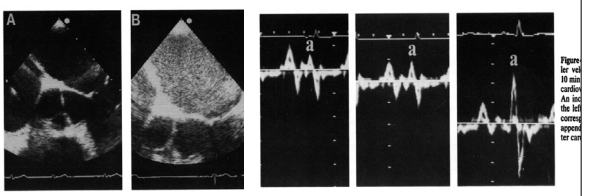
비판막질환: Risk factors (CHADS2)

Peri-cardioversion: >2일 or unknown duration

*** 심방세동의 type에 무관**
—paroxysmal, persistent, long-lasting, short-lasting….

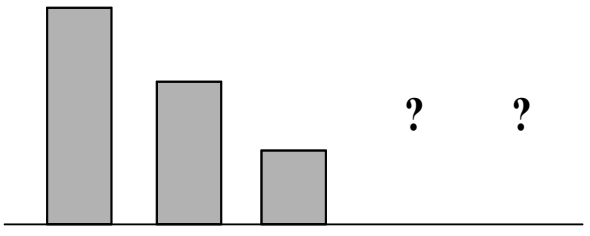
심방세동의 동율동 전환

1. **Transient atrial mechanical dysfunction (stunning) of the LA and LAA) after spontaneous, pharmacological, or electrical conversion of AF or after RFCA of AFL.**
2. **The clustering of thromboembolic events in the first 10 days after cardioversion (98%).**
3. **the atrial stunning after cardioversion of the chronic AFib resolves within 2 to 4 weeks in most patients.**



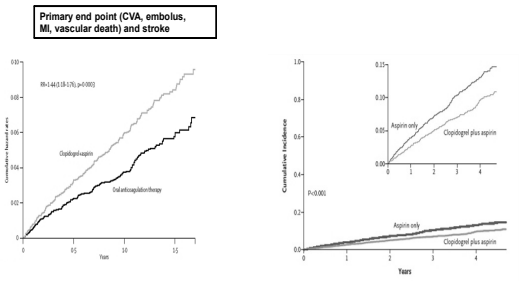
J Am Coll Cardiol 1994;23:307-16
Am J Cardiol 1998;82:1545-7,A8

심방세동 환자에서 아스피린의 효용은?



SPAF IIII, Lancet 1996; 348: 633–38

ACTIVE-W vs. ACTIVE-A trial



Aspirin+Plavix vs. Warfarin
Connolly S. Lancet. 2006;367:1903

Aspirin+Plavix vs. Aspirin
NEJM 2009;360:2066

ESC guideline 2010

Combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily, should be considered for stroke prevention in patients for whom there is patient refusal to take OAC therapy or a clear contraindication to OAC therapy (e.g.inability to cope or continue with anticoagulation monitoring), where there is a low risk of bleeding.

현재의 항응고 치료방침

1. 심방세동의 type, 지속시간에 무관.
2. 임상적 위험요소에 기반. (CHADS2, CHADS2-VASc)
3. 위험군에서는 아스피린보다는 와파린이 효과적.
4. 아스피린에 클로피도그렐을 추가하는 것이 도움은 되지만 와파린보다는 약함.
5. 기타: 판막 질환(승모판협착증) 환자에서의 심방세동 심율동전환—전3주 후4주 시행

와파린의 단점

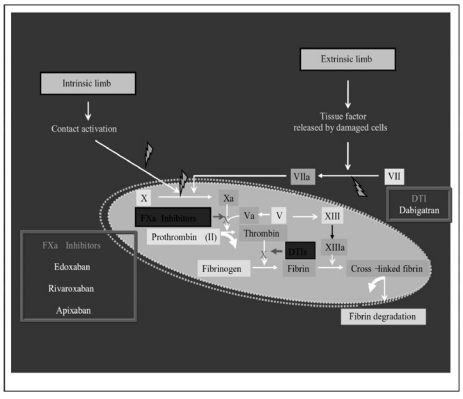
1. INR검사 요망 – 순응도 (교통, 보호자, 경제력…)
2. 음식물, 약물과 상호작용 심하다 – INR수치 변동
3. 반감기가 길다
4. narrow therapeutic window
5. 출혈 (뇌출혈, 소화기 출혈)

Table 1: The RE-LY, AVERROES and ROCKET-AF trials compared. The table is based on preliminary data presented for AVERROES and ROCKET-AF (8, 9).

Trial	RE-LY	AVERROES	ROCKET-AF
Drug and doses	Dabigatran etexilate 150 mg BID or 110 mg BID	Apixaban 5 mg BID	Rivaroxaban 20 mg QD (15 mg QD in patients with creatinine clearance 30–49 ml/min)
Number of patients	18,113	5,600	14,000
Design	Randomised, open label	Randomised, double-blind	Randomised double-blind, double dummy
Condition	AF within 6 months prior randomisation + 1 risk factor	AF within 6 months prior randomisation + 1 risk factor	AF within 6 months prior randomisation + 2 risk factors
Mean age	71.5 years	70 years	73 years
Male:female ratio	63.6 % : 36.4%	58.5% : 41.5%	60%: 40%
Previous stroke / TIA (i.e. secondary prevention subgroup)	20%	13.5%	55%
Mean CHADS$_2$ score	2.1	2.1	3.5
Warfarin naive	50.4%	60.5%	37.5%
Comparator	Dose adjusted warfarin (INR 2.0–3.0, 67% of time in range)	Aspirin (81–324 mg QD)	Dose adjusted warfarin (INR 2.0–3.0, 57.8% of time in range)
Primary endpoint: Stroke and systemic embolism (in % per year)	1.71% warfarin 1.54% dabigatran 110 mg (p=0.34) 1.11% dabigatran 150 mg (p<0.001)	3.9% aspirin 1.7% apixaban (p<0.001)	2.42% warfarin 2.12% rivaroxaban (p=0.117)
Major bleeding events	3.57% warfarin 2.87% dabigatran 110 mg (p=0.003) 3.32% dabigatran 150 mg (p=0.31)	1.2% aspirin 1.4% apixaban (p=0.33)	3.45% warfarin 3.6% rivaroxaban (p=0.576)
ICH (in % per year)	0.74% warfarin 0.23% dabigatran 110 mg (p<0.001) 0.3% dabigatran 150 mg (p<0.001)	0.3% aspirin 0.4% apixaban (p=0.83)	0.74% warfarin 0.49% rivaroxaban (p=0.019)
Comment	Dabigatran 110 mg non-inferior to warfarin with 20% less major bleeding events and significantly less ICH Dabigatran 150 mg superior to warfarin with similar rate of major bleeding and significantly less ICH	Apixaban superior to aspirin, with similar rate of major bleeding (and ICH) and better tolerated (with less discontinuations)	Rivaroxaban non-inferior to warfarin, with non-significant superiority on intention to treat analysis, but superiority achieved with on-treatment analysis

ICH = intracranial haemorrhage; INR = international normalised ratio; TIA = temporary ischaemic attack.

Thromb Haemost 2011; 105: 574–578

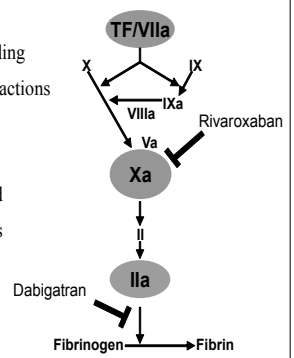


: warfarin

Journal of Cardiovasc Pharm Ther 15(3) 210-219

Dabigatran

1. A competitive inhibitor of thrombin
2. Bioavailability 6.5%; low protein binding
3. No known food or CYP450 drug interactions
4. No need for INR monitoring
5. Hepatotoxicity <1%
6. Half-life: 8 hours after single dose and 14-17 hours after multiple doses
7. BID dosing
8. 80% renal excreted



Curr Treat Cardiovasc Med. 2008;10(5):388-397

Adapted from Weitz *et al*, 2005; 2008

Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial

Summary

Background Effectiveness and safety of warfarin is associated with the time in therapeutic range (TTR) with an international normalised ratio (INR) of 2·0–3·0. In the Randomised Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, dabigatran versus warfarin reduced both stroke and haemorrhage. We aimed to investigate the primary and secondary outcomes of the RE-LY trial in relation to each centre's mean TTR (cTTR) in the warfarin population.

Methods In the RE-LY trial, 18 113 patients at 951 sites were randomly assigned to 110 mg or 150 mg dabigatran twice daily versus warfarin dose adjusted to INR 2·0–3·0. Median follow-up was 2·0 years. For 18 424 patients at 906 sites, the cTTR was estimated by averaging TTR for individual warfarin-treated patients calculated by the Rosendaal method. We compared the outcomes of RE-LY across the three treatment groups within four groups defined by the quartiles of cTTR. RE-LY is registered with ClinicalTrials.gov, number NCT00262600.

Findings The quartiles of cTTR for patients in the warfarin group were less than 57·1%, 57·1–65·5%, 65·5–72·6%, and greater than 72·6%. There were no significant interactions between cTTR and prevention of stroke and systemic embolism with either 110 mg dabigatran (interaction p=0·89) or 150 mg dabigatran (interaction p=0·20) versus warfarin. Neither were any significant interactions recorded with cTTR with regards to intracranial bleeding with 150 mg dabigatran (interaction p=0·71) or 150 mg dabigatran (interaction p=0·09) versus warfarin. There was a significant interaction between cTTR and major bleeding when comparing 150 mg dabigatran with warfarin (interaction p=0·03), with less bleeding events at lower cTTR but similar events at higher cTTR, whereas rates of major bleeding were lower with 110 mg dabigatran than with warfarin irrespective of cTTR. There were significant interactions between cTTR and effects of both 110 mg and 150 mg dabigatran versus warfarin on the composite of all cardiovascular events (interaction p=0·036 and p=0·0006, respectively) and total mortality (interaction p=0·066 and p=0·052, respectively) with reduced event rates at low cTTR, and similar rates at high cTTR.

Interpretation The benefits of 150 mg dabigatran at reducing stroke, 110 mg dabigatran at reducing bleeding, and both doses at reducing intracranial bleeding versus warfarin were consistent irrespective of centres' quality of INR control. For all vascular events, non-haemorrhagic events, and mortality, advantages of dabigatran were greater at sites with poor INR control than at those with good INR control. Overall, these results show that local standards of care affect the benefits of use of new treatment alternatives.

Funding Boehringer Ingelheim.

Rivaroxaban

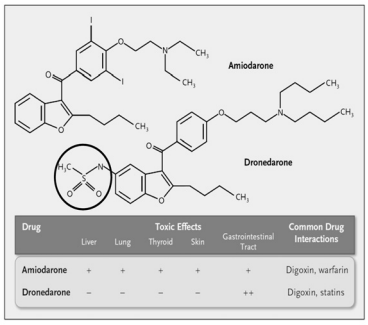
1. Efficacy:

- non-inferior to warfarin for prev.of stroke and non-CNS embolism.
- Rivaroxaban was superior to warfarin while pts were taking it
- By intention-to-treat, rivaroxaban was non-inferior to warfarin but did not achieve superiority.

2. Safety:

- Similar rates of bleeding and adverse events.
- Less ICH and fatal bleeding with rivaroxaban.

Dronedarone: A new antiarrhythmic drug



Drug	Toxic Effects					Common Drug Interactions
	Liver	Lung	Thyroid	Skin	Gastrointestinal Tract	
Amiodarone	+	+	+	+	+	Digoxin, warfarin
Dronedarone	–	–	–	–	++	Digoxin, statins

N Engl J Med 2009: 360;18

iodine radical
methane sulfonyl radical

반감기

전신독성 (간, 폐, 갑상선)
Torsade de Pointes

심방세동의 심박수 조절
발작성 심방세동 예방

심한 심부전 환자에서는 금기

심혈관계 사망을 감소시킨
유일한 부정맥제

Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation

Stefan H. Hohnloser, M.D., Harry J.G.M. Crijns, M.D., Martin van Eickels, M.D., Christophe Gaudin, M.D., Richard L. Page, M.D., Christian Torp-Pedersen, M.D., and Stuart J. Connolly, M.D., for the ATHENA Investigators*

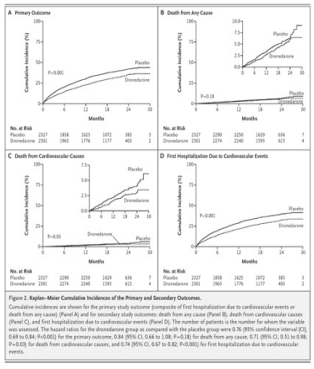


Figure 2. Kaplan–Meier Cumulative Incidences of the Primary and Secondary Outcomes.

Cumulative incidences are shown for the primary study outcome (composite of first hospitalization due to cardiovascular events or death from any cause) (Panel A) and for secondary study outcomes: death from any cause (Panel B), death from cardiovascular causes (Panel C), and first hospitalization due to cardiovascular events (Panel D). The number of patients is the number for whom the variable was assessed. The hazard ratios for the dronedarone group as compared with the placebo group were 0.76 (95% confidence interval [CI], 0.69 to 0.84; P<0.001) for the primary outcome, 0.84 (95% CI, 0.66 to 1.08; P=0.18) for death from any cause, 0.71 (95% CI, 0.51 to 0.98; P=0.03) for death from cardiovascular causes, and 0.74 (95% CI, 0.67 to 0.82; P<0.001) for first hospitalization due to cardiovascular events.

N Engl J Med 2009;360:668-78

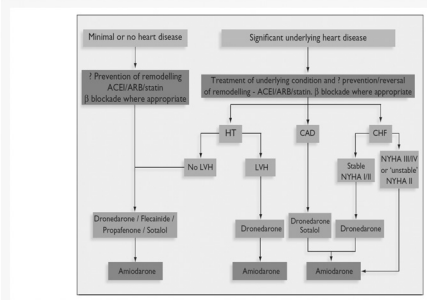
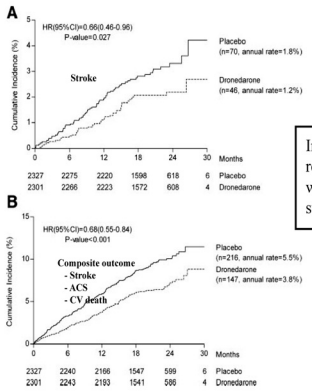


Figure 11 Choice of antiarrhythmic drug according to underlying pathology. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CHF = congestive heart failure; HT = hypertension; LVH = left ventricular hypertrophy; NYHA = New York Heart Association; unstable = cardiac decompensation within the prior 4 weeks. Antiarrhythmic agents are listed in alphabetical order within each treatment box. ? = evidence for 'upstream' therapy for prevention of atrial remodelling still remains controversial.

European Heart Journal 2010, 31:2369

Dronedarone and Thromboembolism

post-hoc analysis

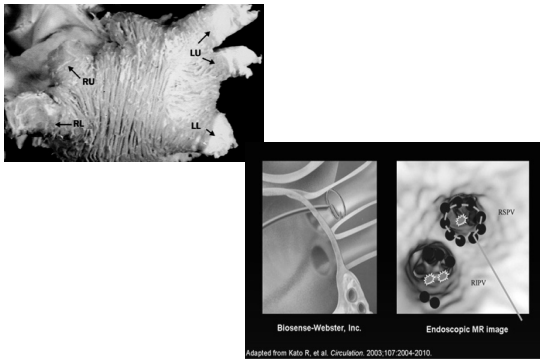


In post hoc analysis of ATHENA, stroke was reduced from 1.8% per year to 1.2% per year with dronedarone, a 34% reduction that was statistically significant.

Circulation. 2009;120:1174-1180

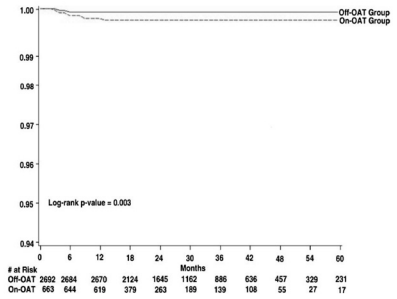
PV musculature

Catheter ablation of AF



Adapted from Kato R, et al. Circulation. 2003;107:2004-2010.

The Risk of Thromboembolism and Need for Oral Anticoagulation After Successful Atrial Fibrillation Ablation



JACC 2010;55:735

Ongoing Trials of Catheter Ablation for AF

CABANA:

Catheter Ablation vs AAD for AF

- NIH/industry-cooperative,
- 5-year study
- mortality (ablation vs. drug therapy)

CASTLE-AF:

Catheter Ablation vs Standard Conventional Tx in Pts with LV Dysfn and AF

- Time to first event of death or hospitalization for HF

Heart Rhythm. 2007;4(6):816-861.
Pacing Clin Electrophysiol. 2009;32(8):987-994.

AF – **Stasis** **Hypercoagulability** **Injury** **– Clots - Stroke**

Drug
RFCA
Maze op

LAA closure

Appendage Obliteration to Reduce Stroke in Cardiac Surgical Patients With Atrial Fibrillation

Thrombi were localized to, or were present in the left atrial appendage and extended into the left atrial cavity in 254 of 446 (57%) of patients with rheumatic atrial fibrillation. In contrast, 201 of 222 (91%) of nonrheumatic atrial fibrillation-related left atrial thrombi were isolated to, or originated in the left atrial appendage ($p < 0.0001$).

These data suggest that left atrial appendage obliteration is a strategy of potential value for stroke prophylaxis in nonrheumatic AF.

(Ann -Thorac Surg 1996;61:755-9)

PLAATO

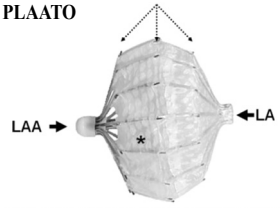
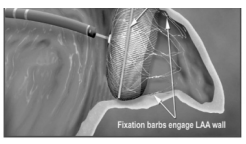
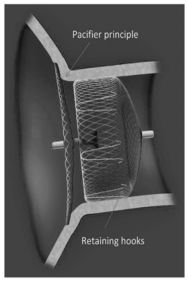


Fig. 1. PLAATO™ device consisting in an expandable nitinol [illegible] an occlusive expanded polytetrafluoroethylene membrane (*) with small anchors along the struts (dot arrows). LAA, side facing left atrial appendage. LA, side facing left atrium. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Watchman

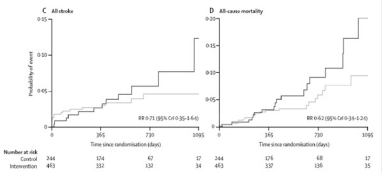


Amplatz



➔ **Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial**

David R Holmes, Vivek Y Reddy, Zoltan G Turi, Shephal K Doshi, Horst Sievert, Maurice Buchbinder, Christopher M Mullin, Peter Sick, for the PROTECT AF Investigators*



	Intervention (n=463)	Control (n=744)
Serious pericardial effusion*	22 (4·8%)	0
Major bleeding†	16 (3·5%)	10 (4·1%)
Procedure-related ischaemic stroke	5 (1·1%)	0
Device embolisation	3 (0·6%)	0
Haemorrhagic stroke‡	1 (0·2%)	6 (2·5%)
Other§	2 (0·4%)	0

*Defined as the need for percutaneous or surgical drainage. †Major bleeding is defined as a bleeding event that required at least 2 units of packed red blood cells or surgery to correct. ‡Of the seven haemorrhagic strokes, six resulted in death (intervention group, n=1; control group, n=5). §An oesophageal tear and a procedure-related arrhythmia.

Table 3: Adverse events

요약

1. 뇌졸중 위험은 심방세동의 type, 지속시간에 무관.
2. 임상적 위험요소에 기반. (CHADS2 score, CHADS2-VASc)
3. 고위험군에서는 반드시 와파린.
4. 최근의 새로 개정된 권고안에 의하면 위험요소가 하나라도 있으면 와파린이 추천됨
5. 아스피린에 클로피도그렐을 추가하는 것이 도움은 되지만 와파린보다는 약함.
6. 단기: 새로운 항응고제 - Dabigatran (direct thrombin inhibitor), Rivaroxaban (factor Xa inhibitor)
   시술(LAA obliteration)
7. 장기: 새로운 항부정맥제(Dronedarone), 도자절제술