



Recurrent stroke under anticoagulation
in patients with mild MS with AF
: prefer LAA occlusion

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Recurrent stroke under anticoagulation in patients with **mild MS with AF**

Stages of MS

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences
A	At risk of MS	<ul style="list-style-type: none"> Mild valve doming during diastole 	Normal transmitral flow velocity	None
B	Progressive MS	<ul style="list-style-type: none"> Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered MVA $>1.5 \text{ cm}^2$ 	<ul style="list-style-type: none"> Increased transmitral flow velocities MVA $>1.5 \text{ cm}^2$ Diastolic pressure half-time $<150 \text{ ms}$ 	<ul style="list-style-type: none"> Mild-to-moderate LA enlargement Normal pulmonary pressure at rest
C	Asymptomatic severe MS	<ul style="list-style-type: none"> Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered MVA $\leq 1.5 \text{ cm}^2$ (MVA $\leq 1.0 \text{ cm}^2$ with very severe MS) 	<ul style="list-style-type: none"> MVA $\leq 1.5 \text{ cm}^2$ (MVA $\leq 1.0 \text{ cm}^2$ with very severe MS) Diastolic pressure half-time $\geq 150 \text{ ms}$ (Diastolic pressure half-time $\geq 220 \text{ ms}$ with very severe MS) 	<ul style="list-style-type: none"> Severe LA enlargement Elevated PASP $>30 \text{ mm Hg}$
D	Symptomatic severe MS	<ul style="list-style-type: none"> Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered MVA $\leq 1.5 \text{ cm}^2$ 	<ul style="list-style-type: none"> MVA $\leq 1.5 \text{ cm}^2$ (MVA $\leq 1.0 \text{ cm}^2$ with very severe MS) Diastolic pressure half-time $\geq 150 \text{ ms}$ (Diastolic pressure half-time $\geq 220 \text{ ms}$ with very severe MS) 	<ul style="list-style-type: none"> Severe LA enlargement Elevated PASP $>30 \text{ mm Hg}$

MS with AF

- **1/3** of embolic events occur **within 1 month** of the onset of AF
- **2/3** of embolic events occur **within 1 year**
- Patients with MS and AF who have experienced an embolic event have **recurrences at a rate of 15~40 events/100 pt-mo.**
- Thrombi in MS appears to be related to the low-flow pattern and have a much more frequent location out of LAA and being often giant.

Medical therapy for MS

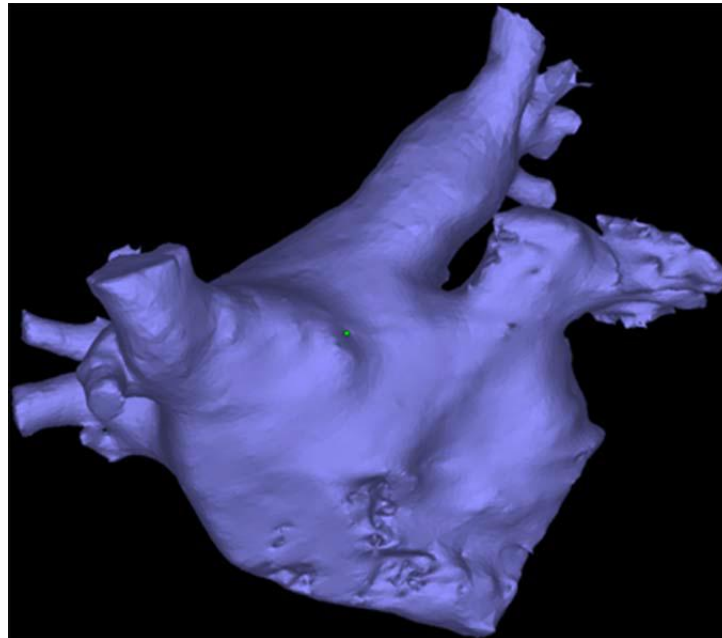
Class I

- **Anticoagulation** (vitamin K antagonist [VKA] or heparin) is indicated in patients with 1) [MS and AF](#) (paroxysmal, persistent, or permanent), or 2) [MS and a prior embolic event](#), or 3) [MS and a left atrial thrombus](#).

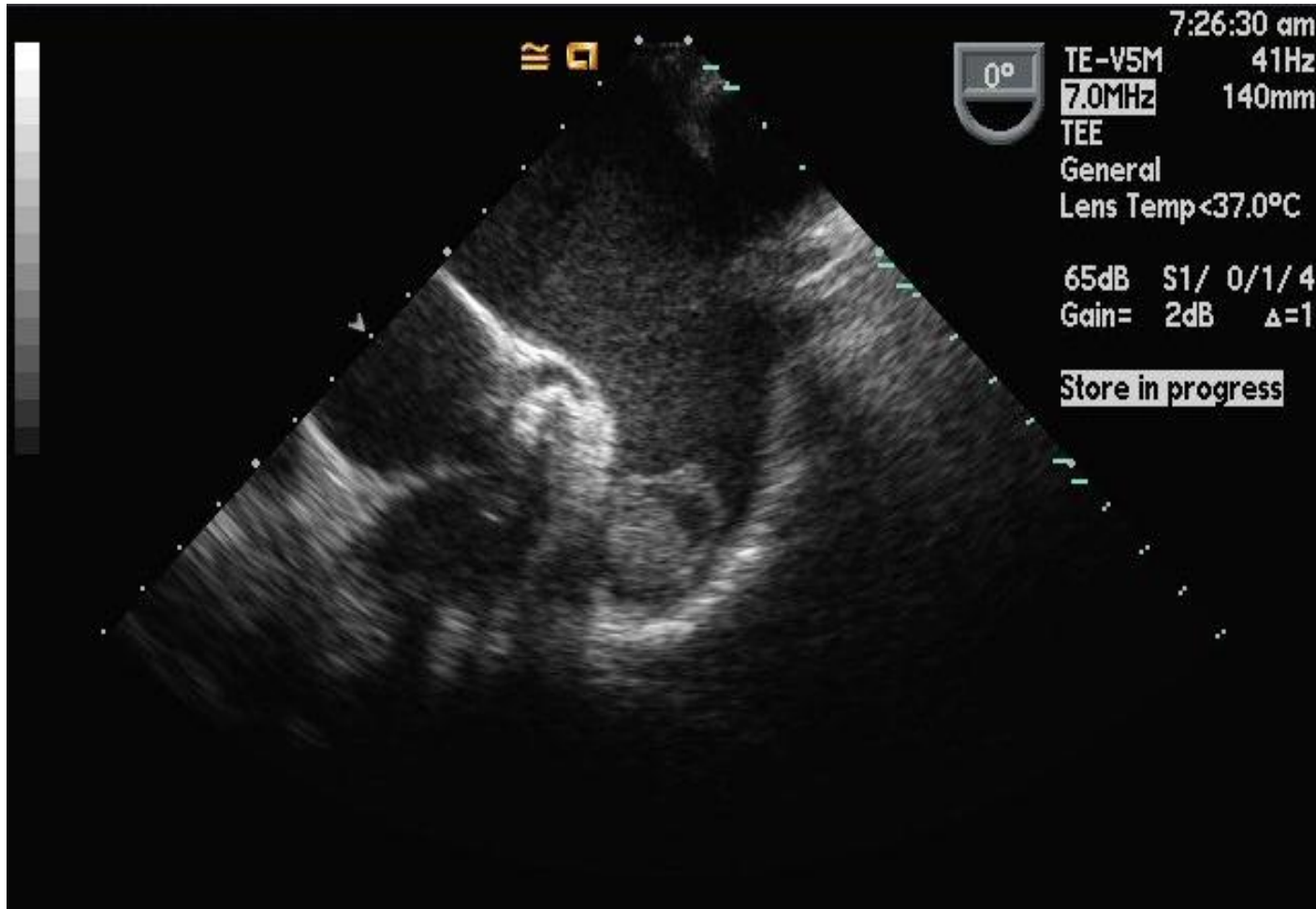
(Level of evidence: B)

LA Appendage

- LAA
 - : a long tubular, hooked structure of variable morphology and size (0.77~19.27 cm)
 - : trabeculated with pectinate muscles and actively contractile
 - : remnant of the original embryonic LA

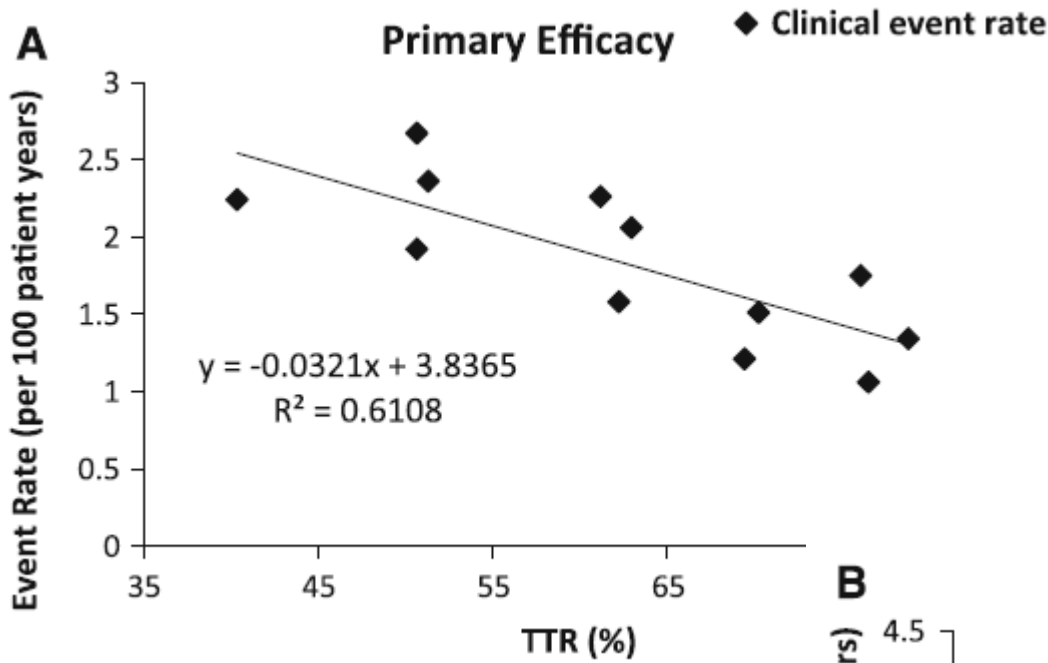


Thrombus in LA Appendage



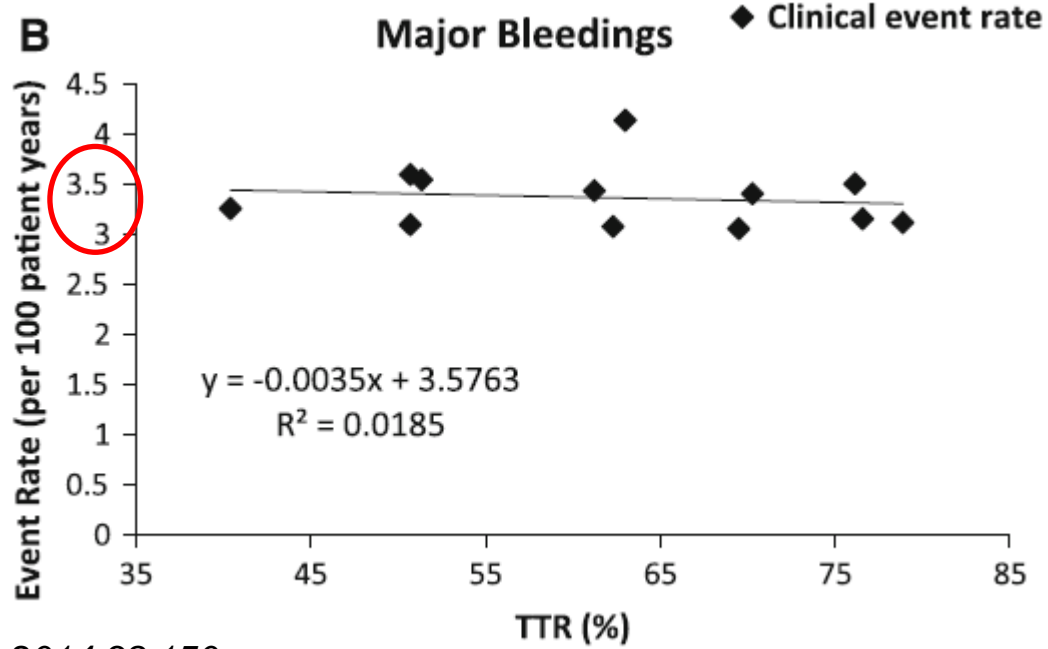
- Stroke or systemic embolism in AF patients
 - : due to **thrombus formation in the LA Appendage (90%)**
- LAA : prone to thrombus formation in AF due to increased blood stasis and extensive trabeculations
- **Oral anticoagulation** is a well established therapy to reduce the risk of stroke in AF patients, but a risk of **bleeding**
- **LAA occlusion** is a possible alternative to oral anticoagulation in the prevention of stroke or systemic embolism in AF

Warfarin's TTR and clinical event rates among warfarin treated NVAF patients



The efficacy of warfarin for reducing stroke risk among NVAF patients was significantly dependent on the TTR of warfarin

The relationship of the bleeding risk with TTR of warfarin was relatively weak.

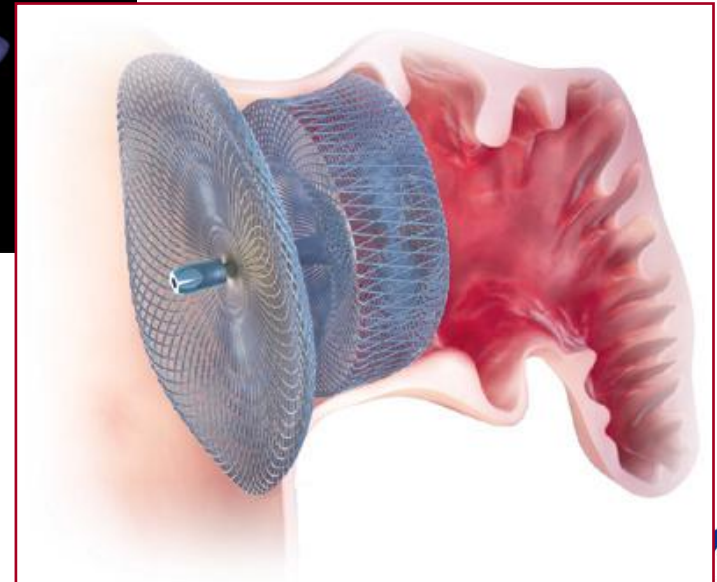
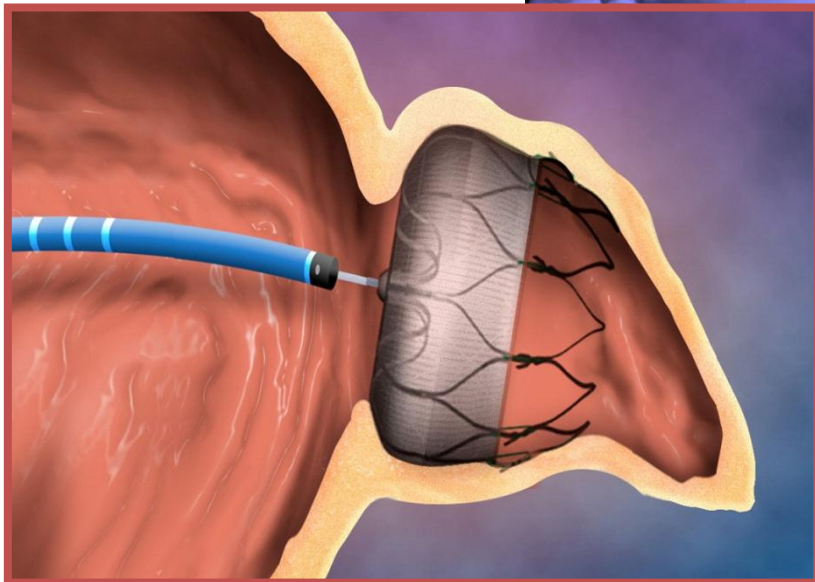
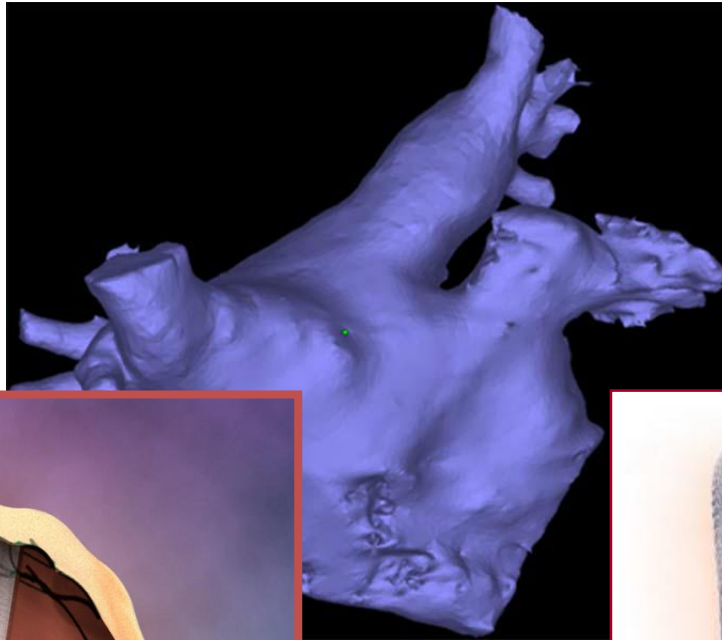


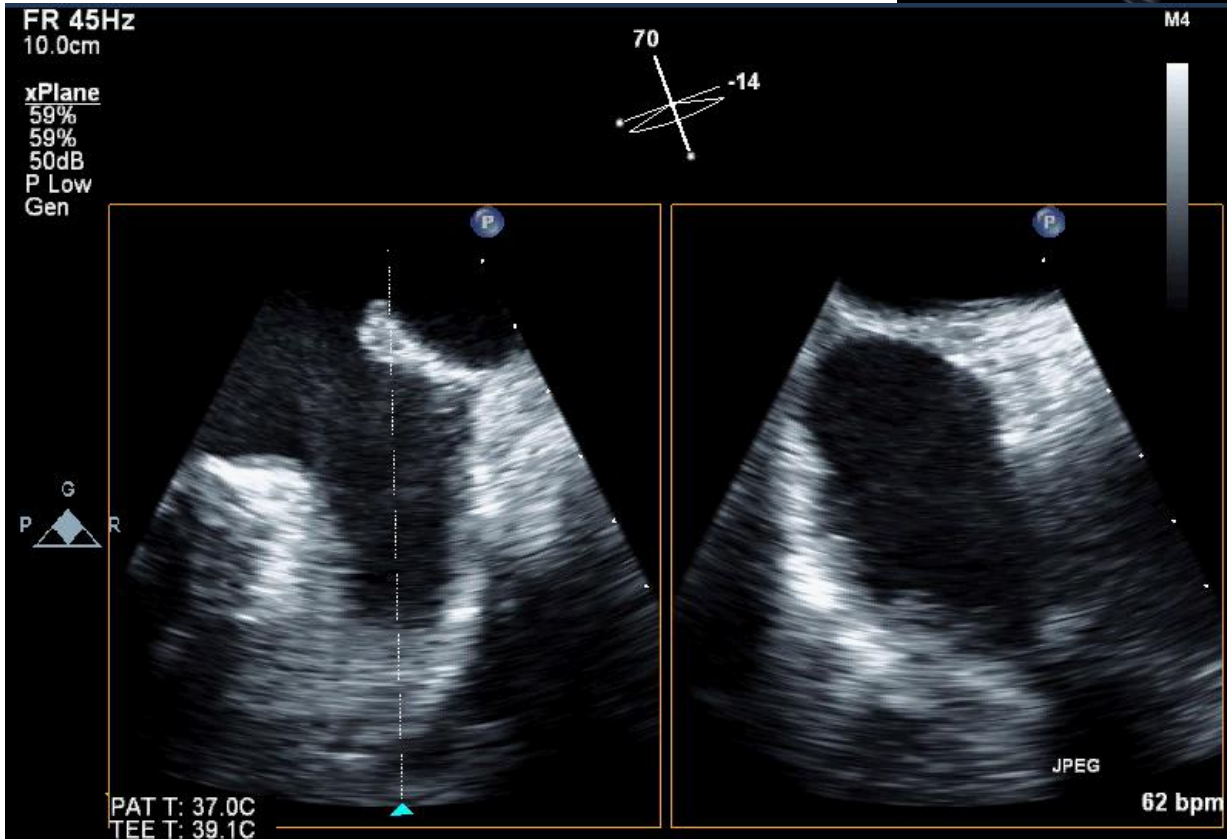
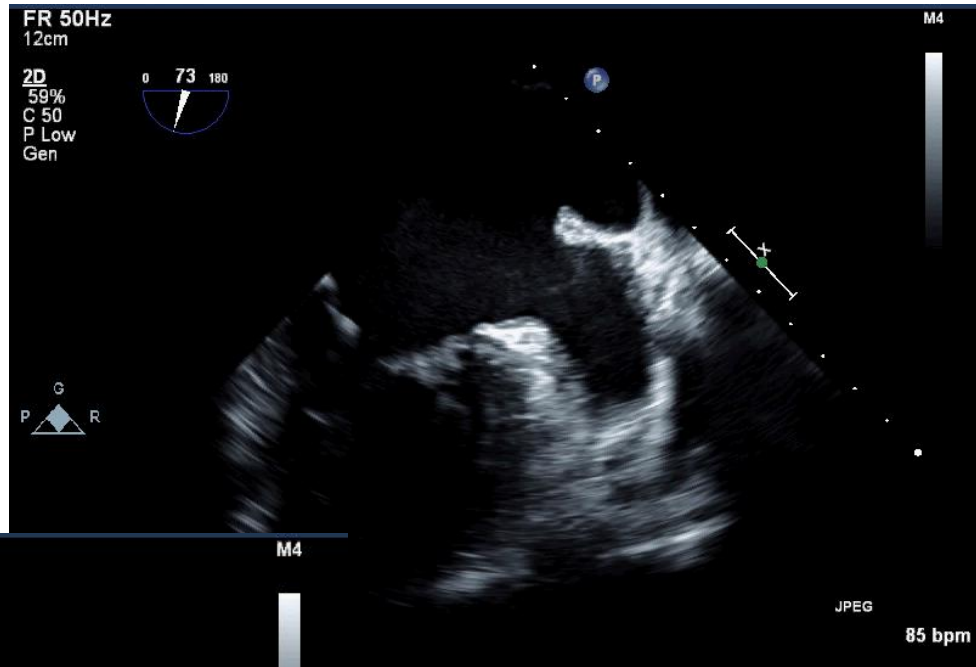
- A. stroke and systemic embolism
- B. Major bleedings

- **LAA occlusion** is a possible alternative to oral anticoagulation in the prevention of stroke or systemic embolism in AF
- **FDA has approved** the use of the **Watchman device** (Boston Scientific, Natick, MA) as an alternative to warfarin OAC based upon data from the PREVAIL and PROTECT-AF trials.
- The **Amplatzer cardiac plug** (St. Jude Medical, St. Paul, MN) or surgical closure with the **AtriClip device** system (AtriCure, West Chester, OH) have shown promise but lack clinical data.

LAA Occlusion

The LAA device reduces the risk of stroke by closing off the LA appendage, which is known to be the main source of blood clots in patients with AF.





Intervention therapy for MS

Class I

- **Percutaneous mitral balloon commissurotomy** for symptomatic patients with severe MS (mitral valve area ≤ 1.5 cm², stage D) and favorable valve morphology in the absence of LA thrombus or moderate-to-severe MR (*Level of Evidence: A*)
- **Mitral valve surgery** (repair, commissurotomy, or valve replacement) for severely symptomatic patients (NYHA class III to IV) with severe MS (mitral valve area ≤ 1.5 cm², stage D) who are not high risk for surgery and who are not candidates for or who have failed previous percutaneous mitral balloon commissurotomy (*Level of Evidence: B*)
- **Concomitant mitral valve surgery** for patients with severe MS (mitral valve area ≤ 1.5 cm², stage C or D) undergoing cardiac surgery for other indications (*Level of Evidence: C*)

Intervention therapy for MS

Class IIa

- **Percutaneous mitral balloon commissurotomy** for asymptomatic patients with severe MS (mitral valve area ≤ 1.5 cm², stage C) and favorable valve morphology in the absence of LA thrombus or moderate-to-severe MR (*Level of Evidence: C*)
- **Mitral valve surgery** for severely symptomatic patients (NYHA class III to IV) with severe MS (mitral valve area ≤ 1.5 cm², stage D), provided there are other operative indications (aortic valve ds, CAD, TR, Ao aneurysm) (*Level of Evidence: C*)

Class IIb

- **Mitral valve surgery and excision of the LA appendage** for patients with severe MS (mitral valve area ≤ 1.5 cm², stages C and D) who have had recurrent embolic events while receiving adequate anticoagulation (*Level of Evidence: C*)

Recurrent stroke under anticoagulation in patients with **mild MS with AF**

Consider

- : increase INR level 2.5~3.5
- : change to NOAC (Non-vitamin K Oral Anticoagulant)
- : implant the LAA occlusion device
- : surgical procedure of mini-maze

Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF (PROTECT AF)

First prospective randomized clinical trial of LAA closure device

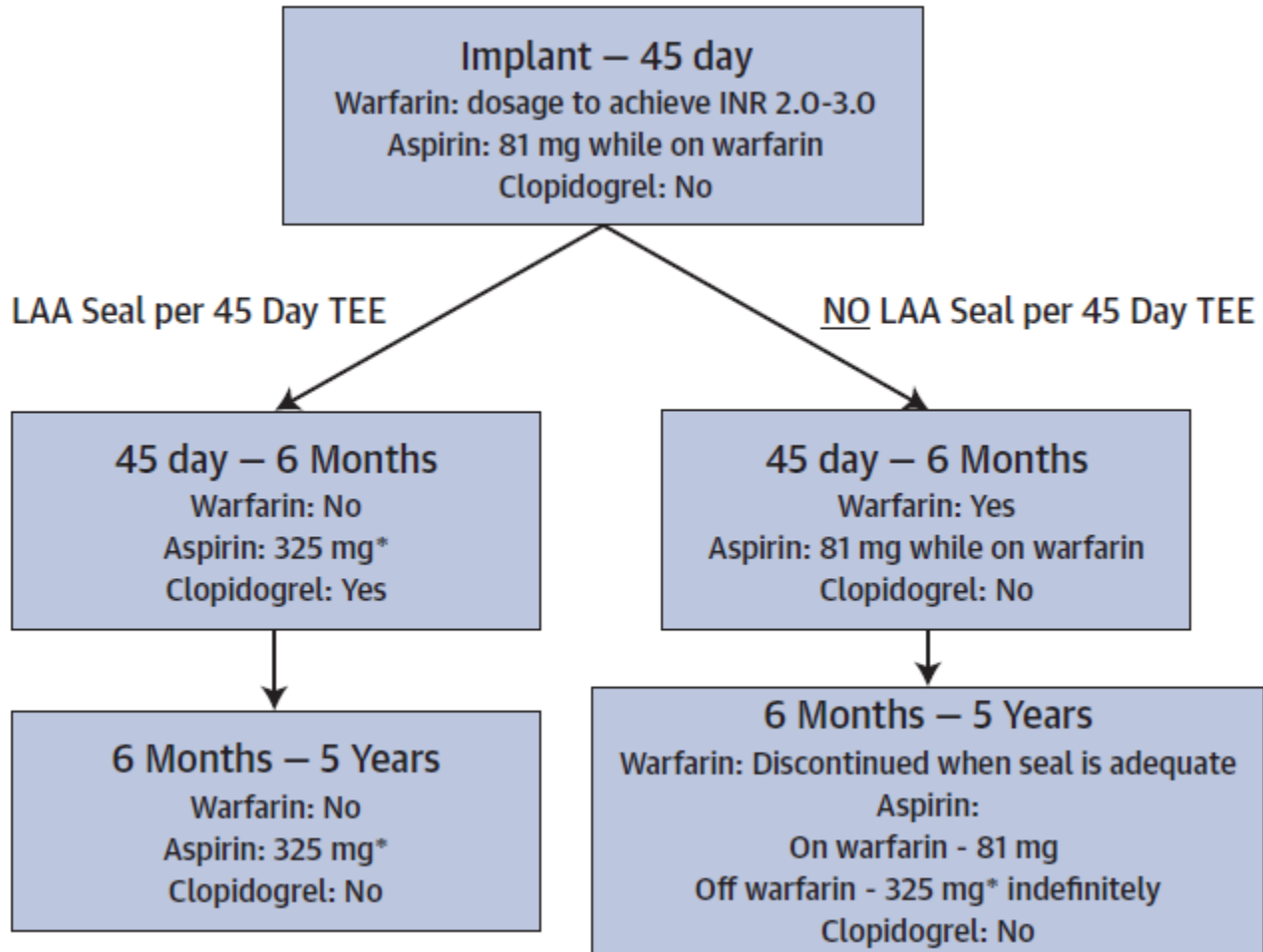
Study Objective:	Evaluate the efficacy and safety of the WATCHMAN LAA Closure Device as compared to long-term warfarin therapy in patients with non-valvular atrial fibrillation and CHADS ₂ score ≥ 1
Study Design:	Prospective, randomized (2 Device: 1 Control), non-inferiority study of the Watchman device compared to long-term warfarin therapy
Primary Endpoint:	Non-inferiority of the WATCHMAN device to warfarin therapy for the composite of ischemic stroke, hemorrhagic stroke, systemic embolism and cardiovascular/unexplained death
Additional Endpoints:	Life-threatening events including device embolization requiring retrieval, pericardial effusion requiring intervention, cranial and GI bleeding, and bleeding requiring transfusion ≥ 2 units PRBCs
Patient Population:	WATCHMAN n=463 Control n=244 Roll-in n=93
Number of Sites:	59 (55 U.S., 4 EU)

Holmes DR, et al. *Lancet* 2009; 374: 534

Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF (**PROTECT AF**)

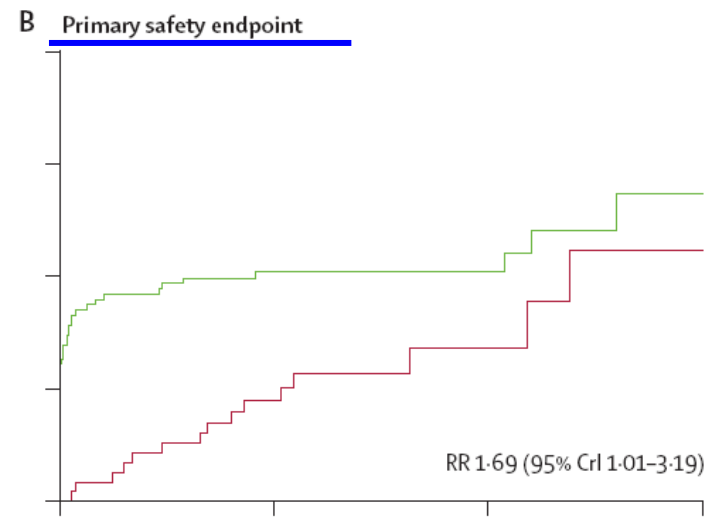
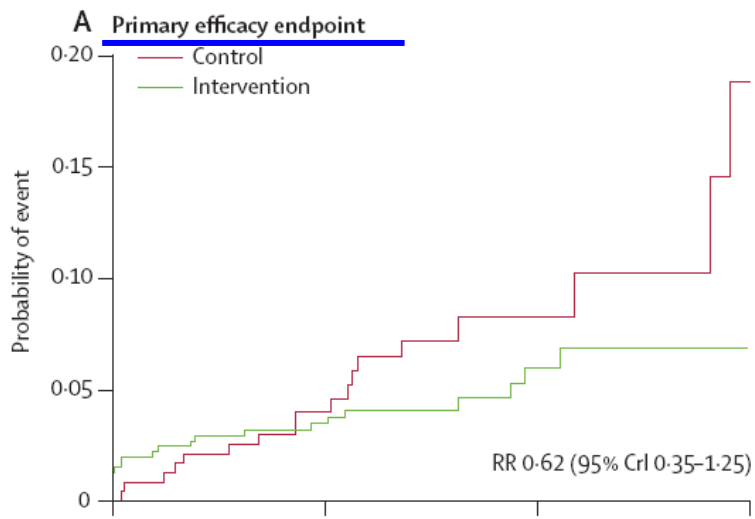
Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Age >18 years, • Nonvalvular AF (paroxysmal, persistent, or permanent), • CHADS2 score ≥ 1, 	<ul style="list-style-type: none"> • Contraindications to warfarin, • Comorbidities other than atrial fibrillation that required chronic warfarin use, • LAA thrombus, • Patent foramen ovale with atrial septal aneurysm and right-to-left shunt, • Mobile aortic atheroma, • Symptomatic carotid artery disease, • LVEF < 30%, • Significant mitral stenosis,

Post-implant protocol-specified medication requirements and warfarin cessation requirements

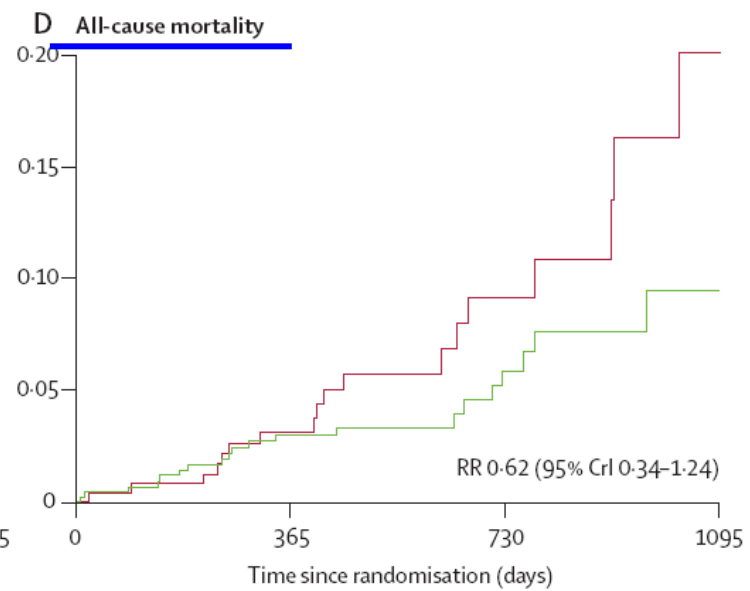
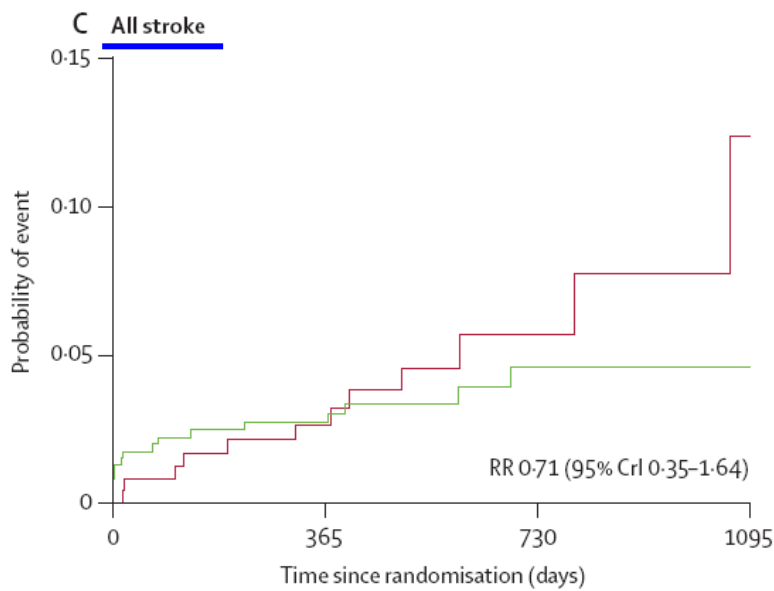


seal defined as TEE

documented residual peridevice flow <5 mm in width and no definite visible large thrombus on the device



The efficacy of percutaneous closure of the LAA was noninferior to warfarin therapy.



Number at risk		0	365	730	1095	0	365	730	1095
Control	244	174	67	17	244	176	68	17	
Intervention	463	332	132	34	463	337	136	35	

Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF (**PROTECT AF**)

- The **primary efficacy event rate**
 - 3% per patient-year in the Watchman device arm
 - 4.3% per patient-year in the warfarin arm (RR 0.71, 95% CI 0.44–1.3)
- The **primary safety events**
 - 5.5% per patient-year in the Watchman device arm
 - 3.6% per patient-year in the warfarin arm (RR 1.52, 95% CI 0.95–2.7)
- The majority of adverse safety events in the Watchman arm were driven by peri-procedural events.
- After the peri-procedural period, adverse safety events did occur more frequently in the warfarin arm.

Prospective Randomized Evaluation of the Watchman LAA Closure Device in patients with AF vs Long-term warfarin therapy (**PREVAIL**)

- Designed to investigate the concerns from the PROTECT-AF trial
- **20%** of enrolling centers implanting physicians were required to have no prior experience in implanting the Watchman device.
- 50 centers, **407 patients** in a 2:1 ratio of device to control
- The first primary efficacy endpoint : a combined of stroke, CV or unexplained death, and systemic thromboembolism over 18 months
- The second primary efficacy endpoint : ischemic stroke and systemic thromboembolism **from 8 days** after randomization over 18 months
- The primary composite safety endpoint : all cause mortality, ischemic stroke, systemic thromboembolism, device or procedure related events requiring open cardiac surgery, major endovascular intervention **between** randomization, 7 days of the procedure, or hospital discharge, whichever was later

Prospective Randomized Evaluation of the Watchman LAA Closure Device in patients with AF vs Long-term warfarin therapy (**PREVAIL**)

Inclusion criteria

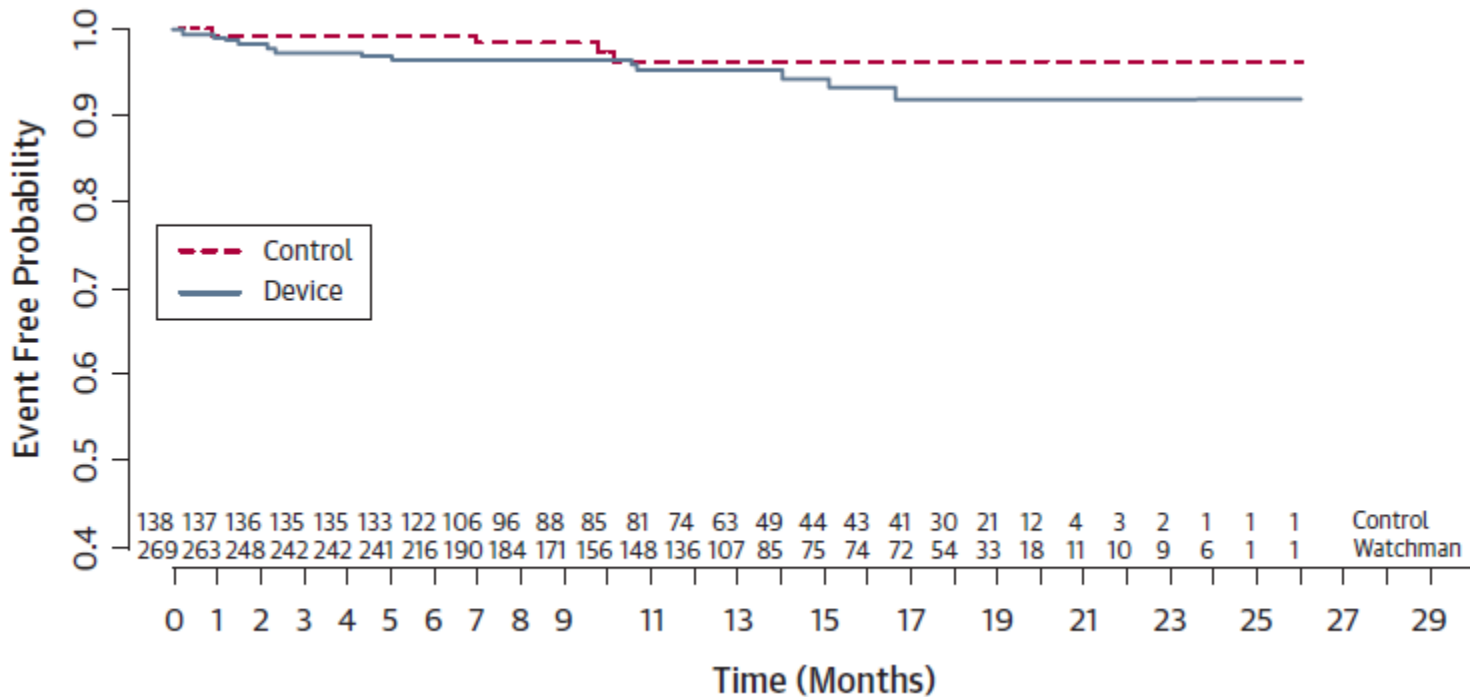
- **Nonvalvular AF** (paroxysmal, persistent, or permanent),
- **CHADS₂ score ≥ 2** or 1 and any following risk factors
female ≥ 75 years, EF $\geq 30\%$ but $< 35\%$, age 65 to 74 years and either diabetes or coronary disease, age ≥ 65 years with heart failure

Exclusion criteria

- **Contraindications to warfarin or aspirin,**
- Comorbidities other than atrial fibrillation that required long-term warfarin use,
- Previous stroke/TIA within 90 days.
- Symptomatic carotid artery disease,
- Patent foramen ovale or atrial septal defect requiring treatment,
- Patients in whom clopidogrel was indicated

Freedom From First Primary Endpoint (Intention-to-Treat) (PREVAIL)

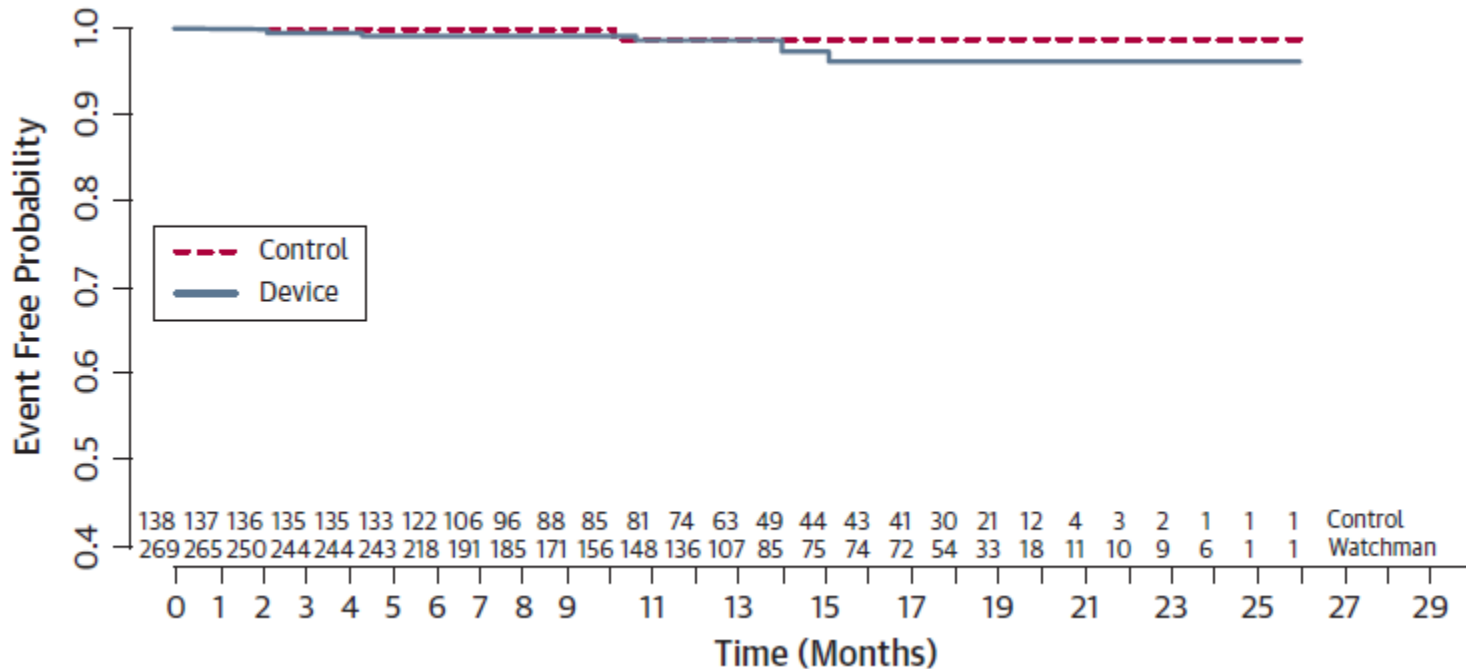
18 month first primary endpoint
 : 6.4% in the device arm and 6.3% in the control arm
 : 1.07 (95% CrI 0.57–1.89)



a combined of stroke, CV or unexplained death, and systemic thromboembolism

Freedom From Second Primary Endpoint (Intention-to-Treat) (PREVAIL)

18 month second primary endpoint
2.53% in the Watchman arm and 2.0% in the control arm



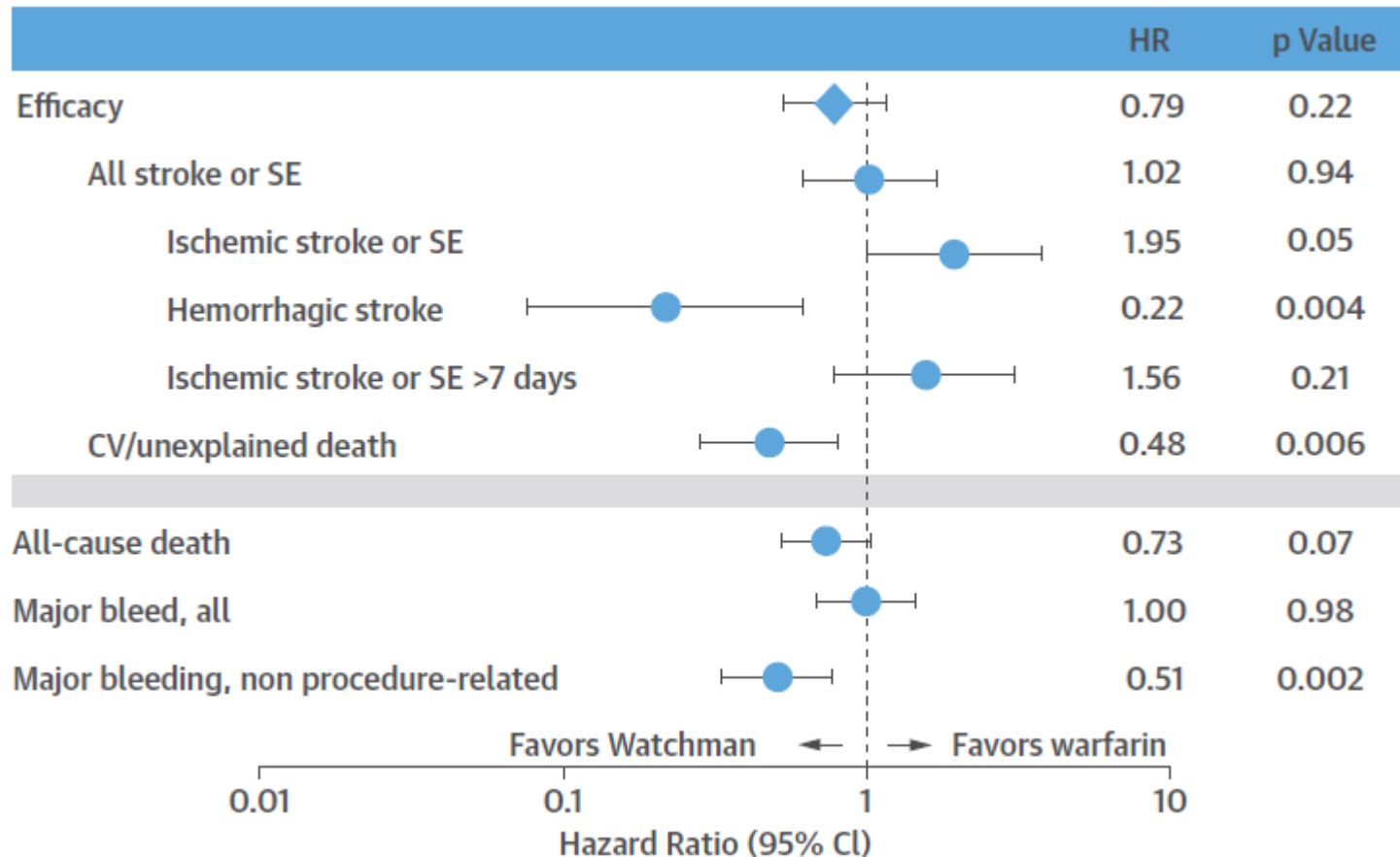
ischemic stroke and systemic thromboembolism **from 8 days** after randomization

Safety Endpoint (Intention-to-Treat) (PREVAIL)

	% (n/N)	95% CrI
Safety primary endpoint results	2.2% (6/269)	2.652%
	No. of Events	% of Subjects
Safety events by type		
Device embolization	2	0.7
Arteriovenous fistula	1	0.4
Cardiac perforation	1	0.4
Pericardial effusion with cardiac tamponade	1	0.4
Major bleed requiring transfusion	1	0.4

PROTECT AF / PREVAIL Combined

The non-inferiority and possible superiority efficacy signal from PROTECT-AF and the acceptable safety signal from PREVAIL



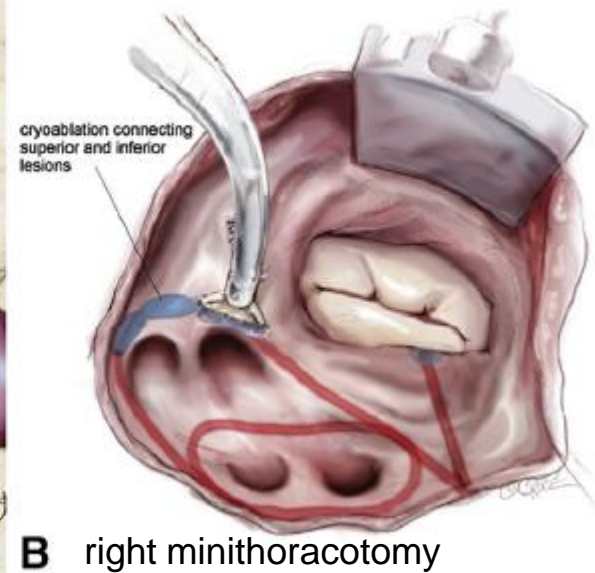
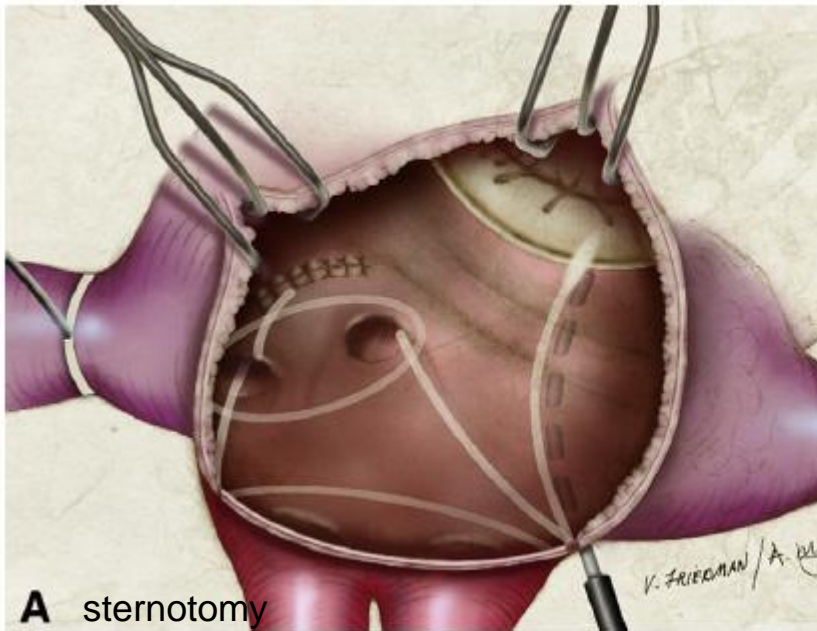
Surgical treatment of AF

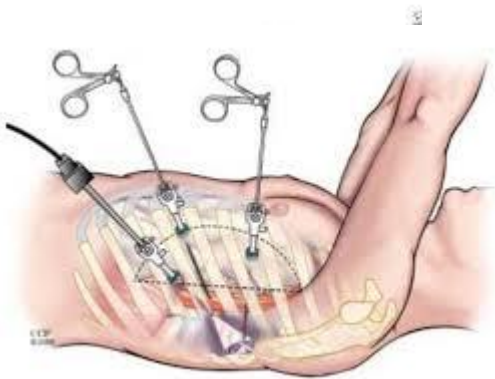
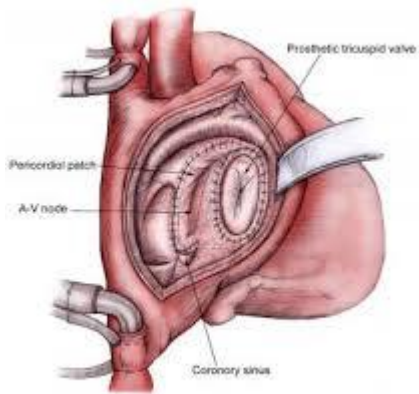
- 48 studies were included comprising 3,832 patients
- the classical 'cut and sew' Cox-Maze III technique and radiofrequency, microwave and cryoablation techniques
- **30-d mortality : 2.1% and 4.2%** (cut and sew technique and alternative sources, p=0.21)

		Alternative sources	CS	P value
Age (yrs; mean)		61.2	55.0	0.005
Duration AF (yrs; mean)		5.4	5.5	0.90
Left atrial size (mm;mean)		55.5	57.8	0.23
LVEF (%; mean)		57	58	0.63
	Chronic AF (%)	92.0	77.1	0.05
	Lone AF (%)	1.6	19.3	0.06
	Biatrial LP (%)	30.3	100	0.00
	Bleeding (%)	4.4	4.9	0.65
	IABP (%)	2.4	2.5	0.87
	CVA (%)	1.6	0.5	0.21
	30-d Mortality (%)	4.2	2.1	0.09
	PM (%)	4.9	5.8	0.21
	SR (%)	78.3	84.9	0.03

Cox maze IV procedure for AF

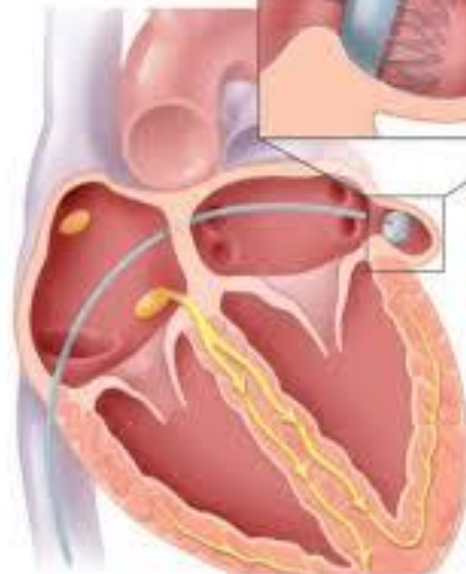
- right minithoracotomy (n=104) and sternotomy (n=252)
- overall complication rate : 6% vs 13%, $p=0.044$
- 30-day mortality : 0% vs 4%, $p=0.039$





Left atrial appendage closure

A device is placed in the left atrial appendage to close it off from the rest of the left atrium.





VS



Recurrent stroke under anticoagulation in patients with **mild MS with AF**

Consider

: *increase INR level 2.5~3.5*

: *change to NOAC (Non-vitamin K Oral Anticoagulant)*

: **implant the LAA occlusion device**

: *surgical procedure of mini-maze*