Patients selection criteria for LAA occlusion

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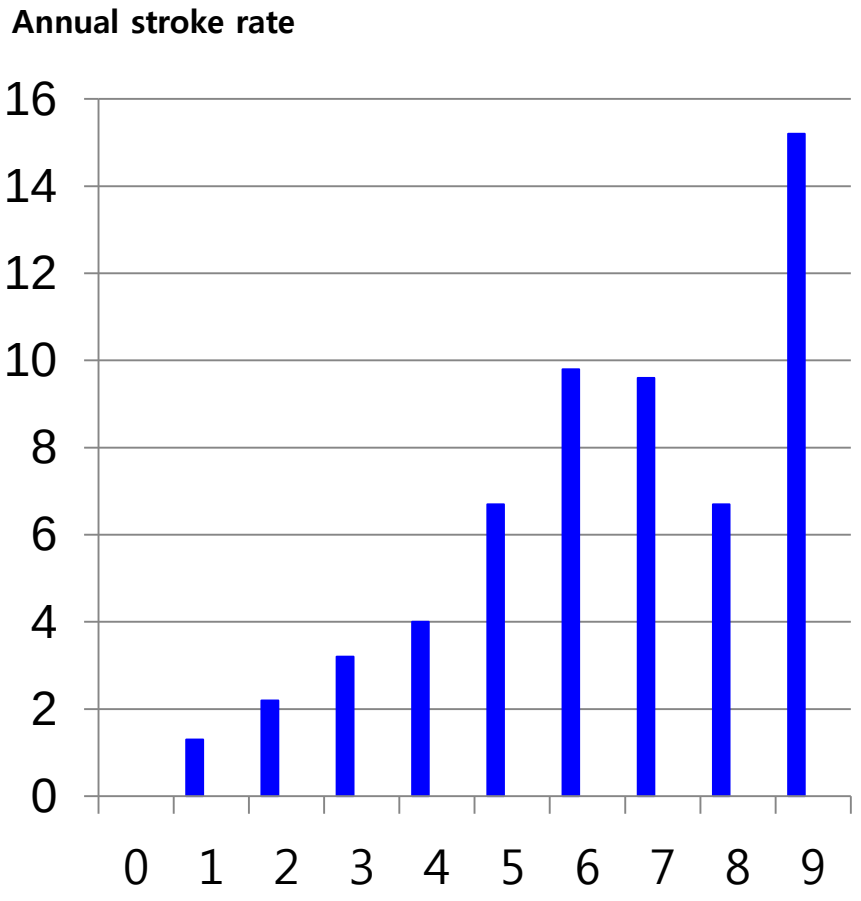
Atrial Fibrillation

- The most common cardiac arrhythmia.
- Confers a 5-fold risk of stroke.
- The rate of ischemic stroke among patients with AF averages 5% per year.
- One of five (20%) of all strokes is attributed to AF.
- The risk of death from AF-related stroke is doubled.

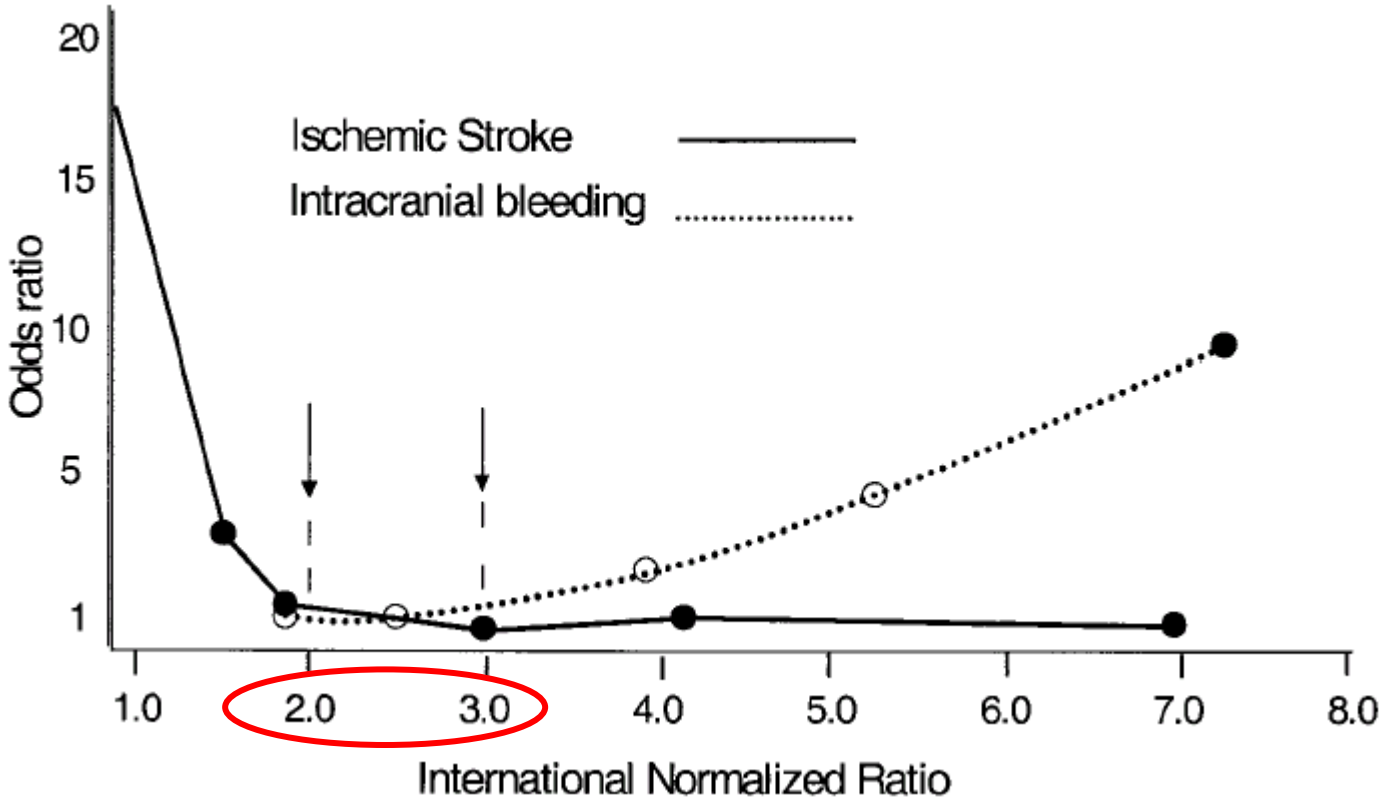
CHA_2DS_2VASc score and stroke rate

Risk factors

- ≥ 75 yrs old (2)
- Previous stroke, TIA, Thromboembolism (2)
- CHF (1)
- HT (1)
- DM (1)
- Vascular disease (1)
- 65~74 yrs old (1)
- Female (1)



Camm AJ, et al. Eur Heart J 2010



- Doubling of the rate of intracranial hemorrhage when the INR exceeds 3.0
- 70% increase in the rate of stroke when the INR is less than 2.0

Stroke vs Bleeding

HAS-BLED bleeding risk score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

Bleeding risk score

- Elderly > 65 yrs old (1)
- Stroke (1)
- Hypertension (1)
- Abnormal renal function (1)
- Abnormal liver function (1)
- Bleeding (1)
- Labile INRs (1)
- Drugs (1)
- Alcohol (1)

Pisters R, et al, Chest 2010

Case 1.

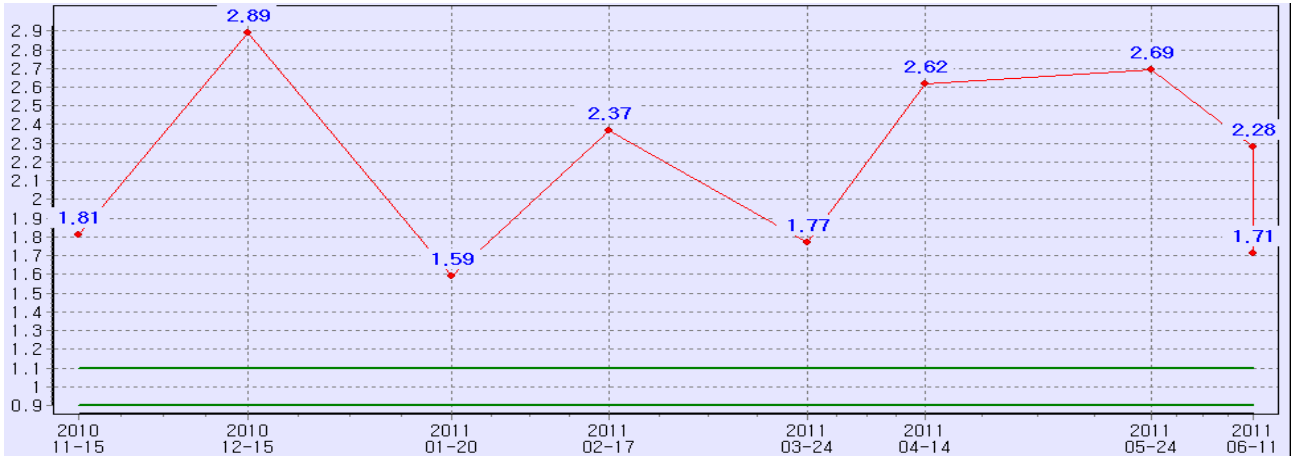
69 yrs old lady

Hypertension, paroxysmal atrial fibrillation

History of stroke (Rt PCA infarction)

She was taking antihypertensive agents, sotalol, warfarin

INR



CHA_2DS_2-VASc score 4	HAS-BLED score 4
• ≥ 75 yrs old (2) • Previous stroke, TIA, Thromboemolism (2) • CHF (1) • HT (1) • DM (1) • Vascular disease (1) • 65~74 yrs old (1) • Female (1)	• Elderly > 65 yrs old (1) • Stroke (1) • Hypertension (1) • Abnormal renal function (1) • Abnormal liver function (1) • Bleeding (1) • Labile INRs (1) • Drugs (1) • Alcohol (1)

Right cerebellar ICH

Case 2

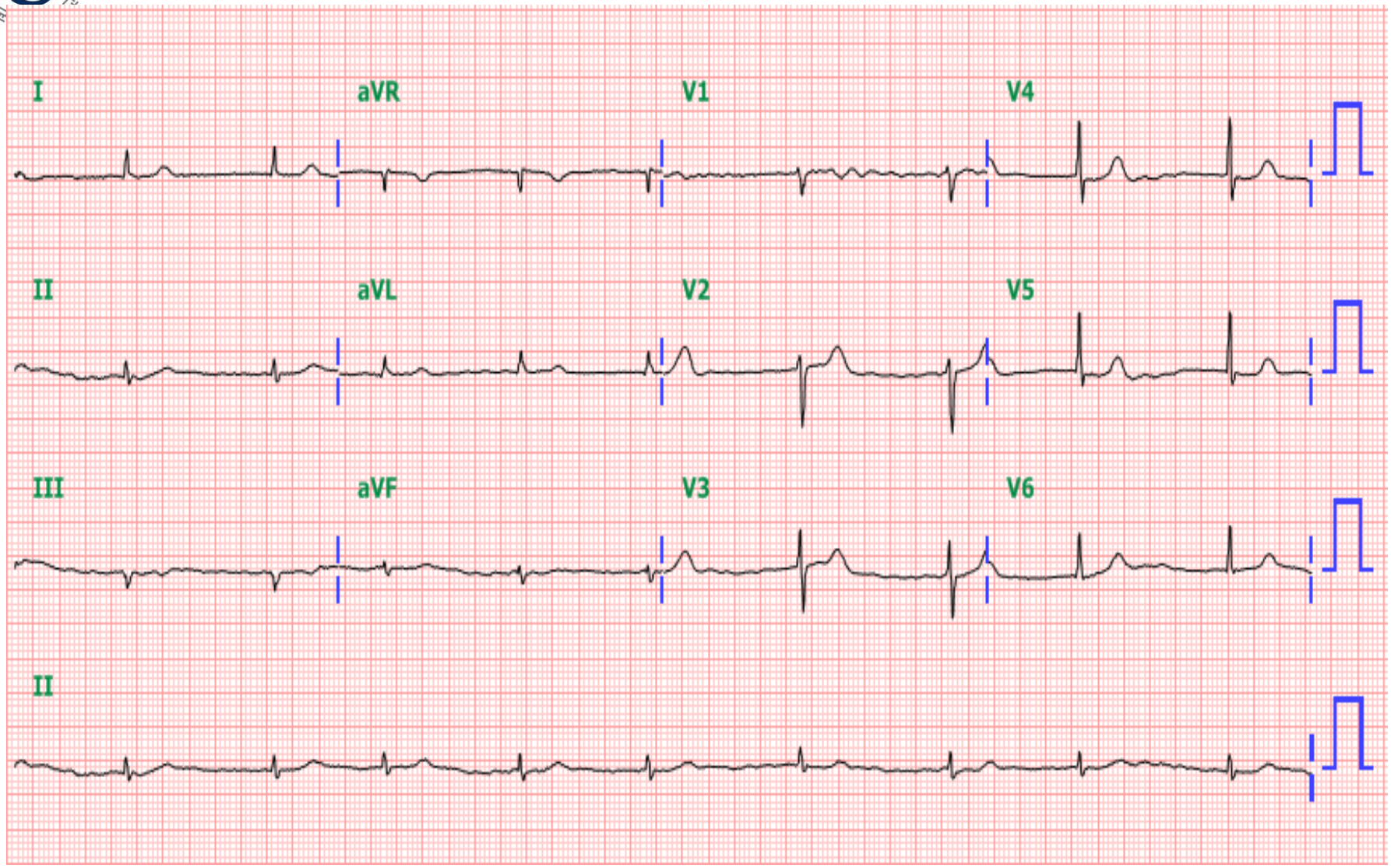
84 yrs old gentlemen

Hypertension, Atrial fibrillation, EF 56%, LA 47 mm

History of GI bleeding

He was taking antihypertensive agent and aspirin

Stroke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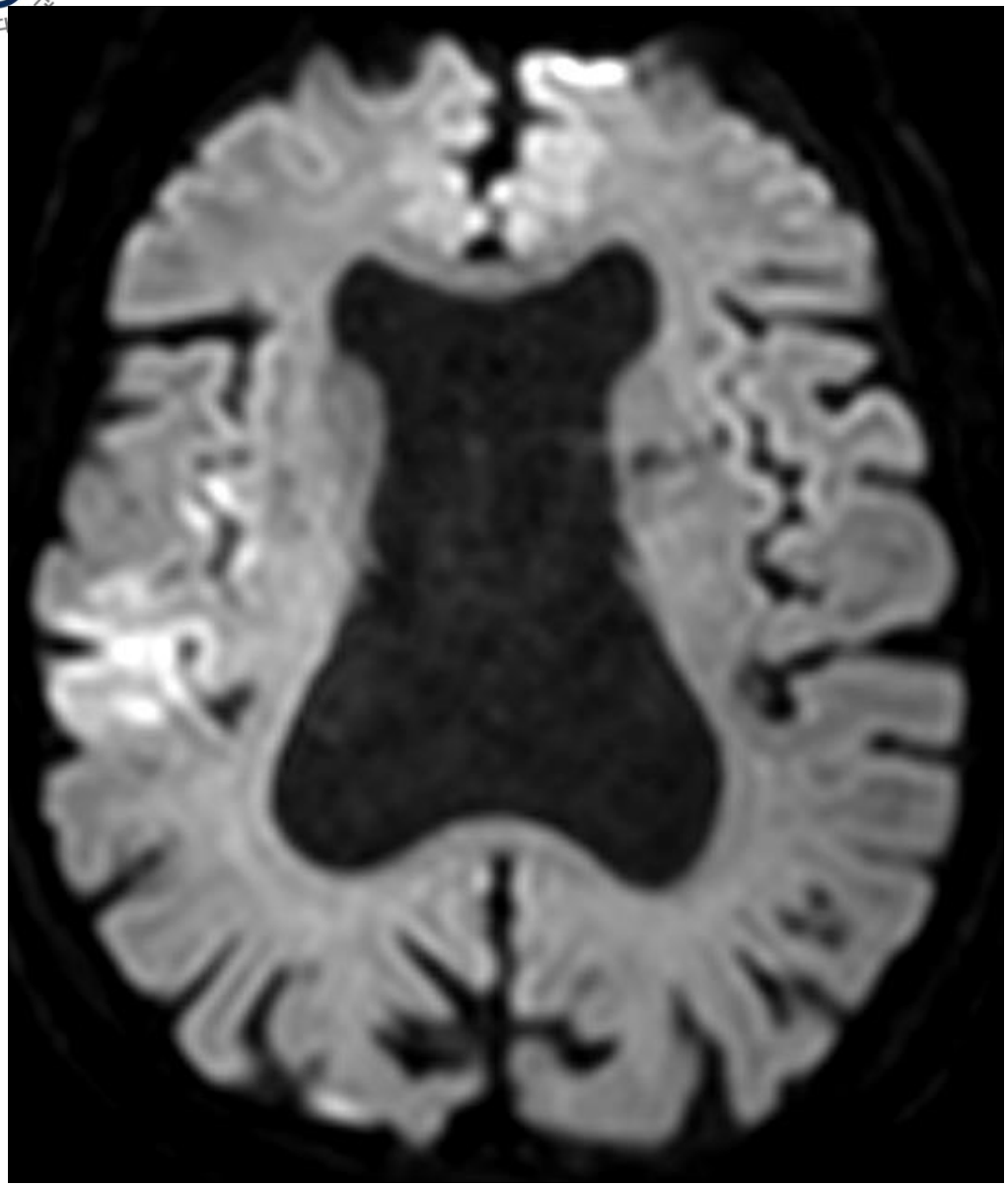
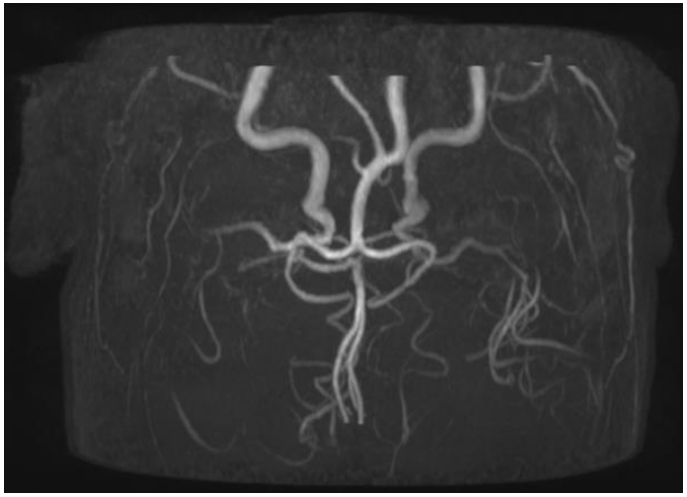
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II



- Acute infarction, right MCA territory.
- Occlusion of inferior division of right MCA.



CHA_2DS_2-VASc score 5	HAS-BLED score 4
• ≥ 75 yrs old (2) • Previous stroke, TIA, Thromboemolism (2) • CHF (1) • HT (1) • DM (1) • Vascular disease (1) • 65~74 yrs old (1) • Female (1)	• Elderly > 65 yrs old (1) • Stroke (1) • Hypertension (1) • Abnormal renal function (1) • Abnormal liver function (1) • Bleeding (1) • Labile INRs (1) • Drugs (1) • Alcohol (1)

Question :

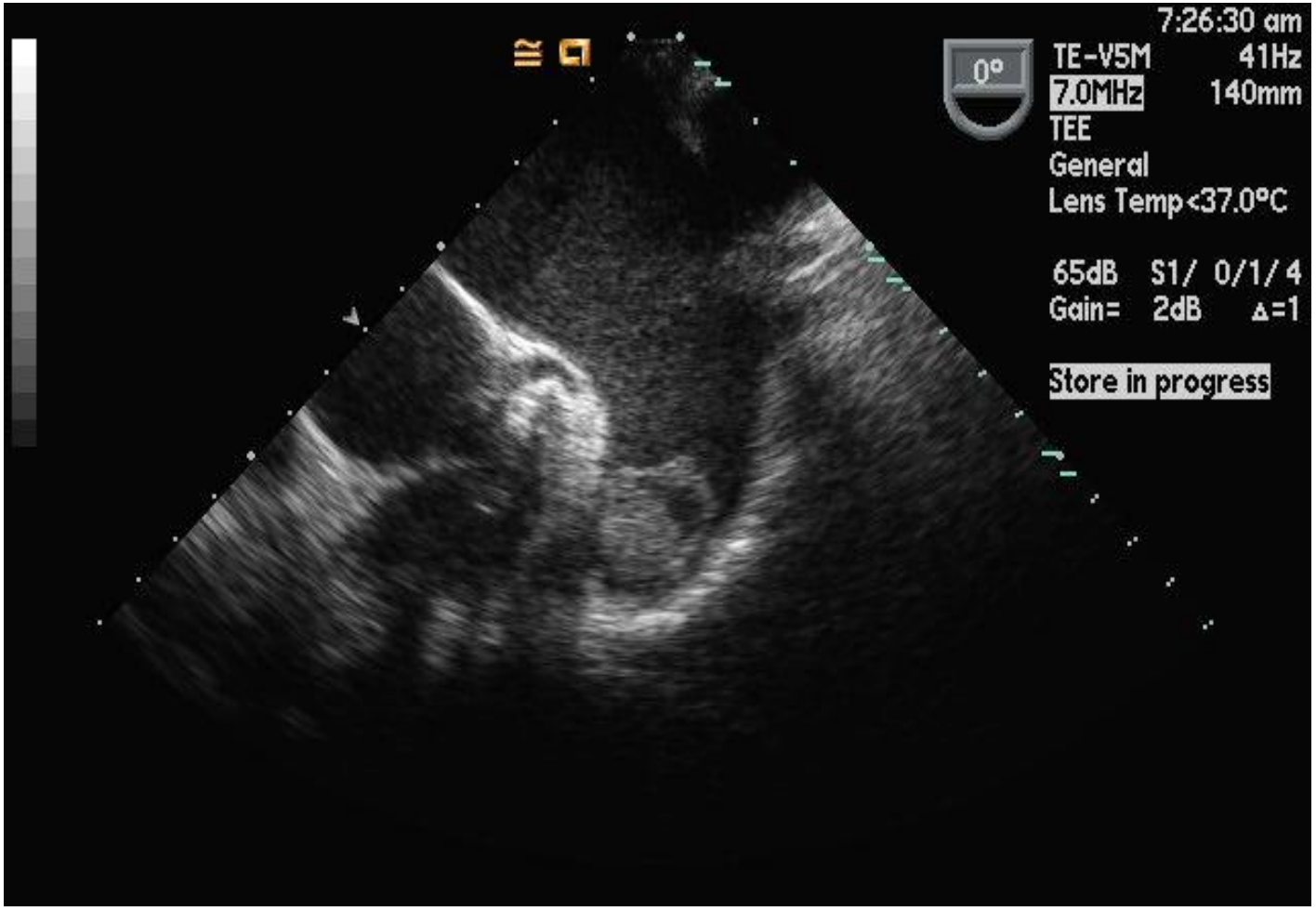
Which of the following treatment for AF would you choose?

1. **No further treatment**
2. **Consider warfarin**
3. **Consider new anticoagulant**
4. **Rhythm control: AF ablation**
5. **Consider LAA closure**

Stroke Prevention in AF patients

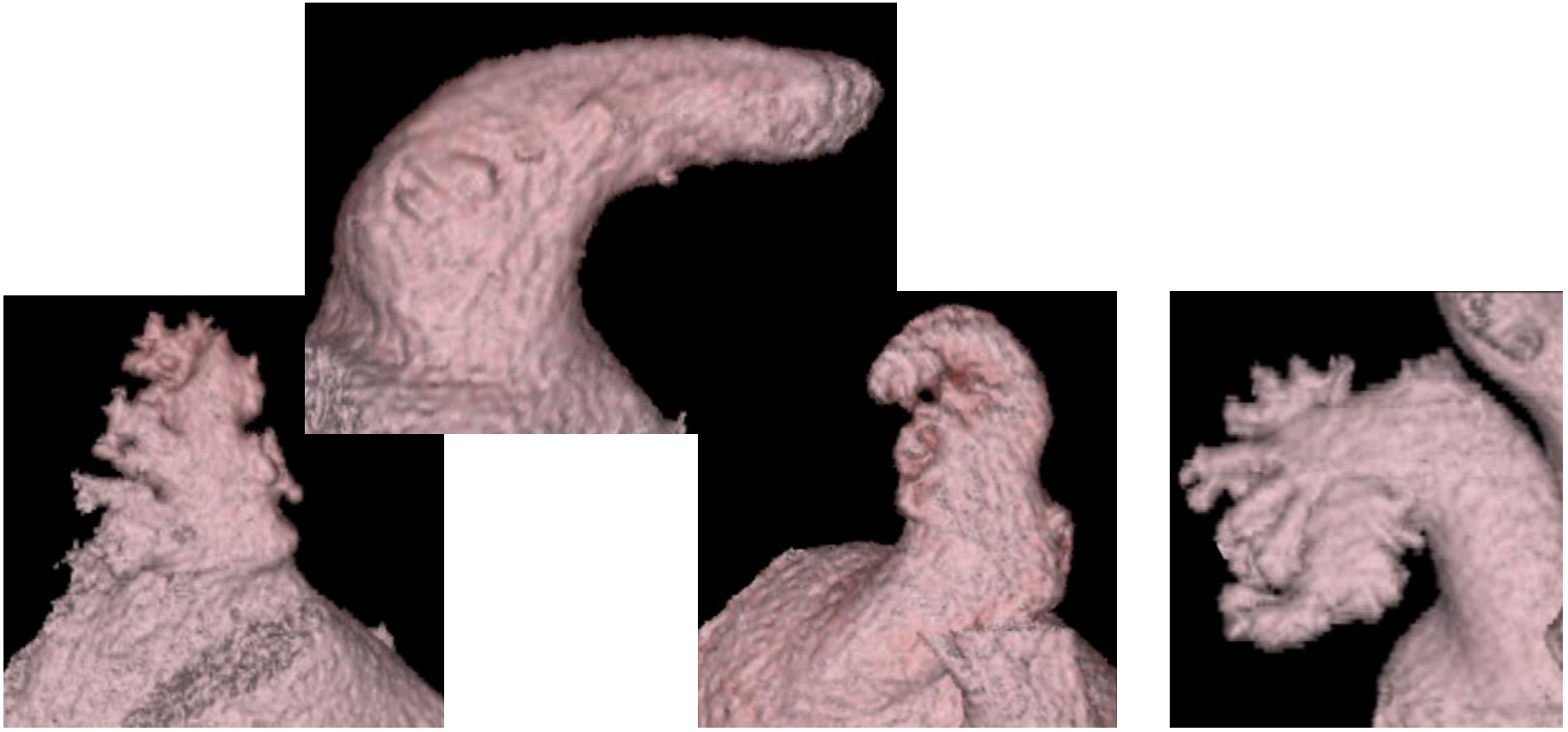
- **Oral anticoagulation** with vitamin-K-antagonists is the standard medical therapy for stroke prevention in patients with AF.
- Chronic therapy with vitamin-K-antagonists is ***contraindicated*** in 14~44% of patients with AF who are at risk for stroke.
- The **benefits of oral anticoagulation** with vitamin-K-antagonists are **limited** by underutilization, narrow therapeutic window and increased risk for bleeding.

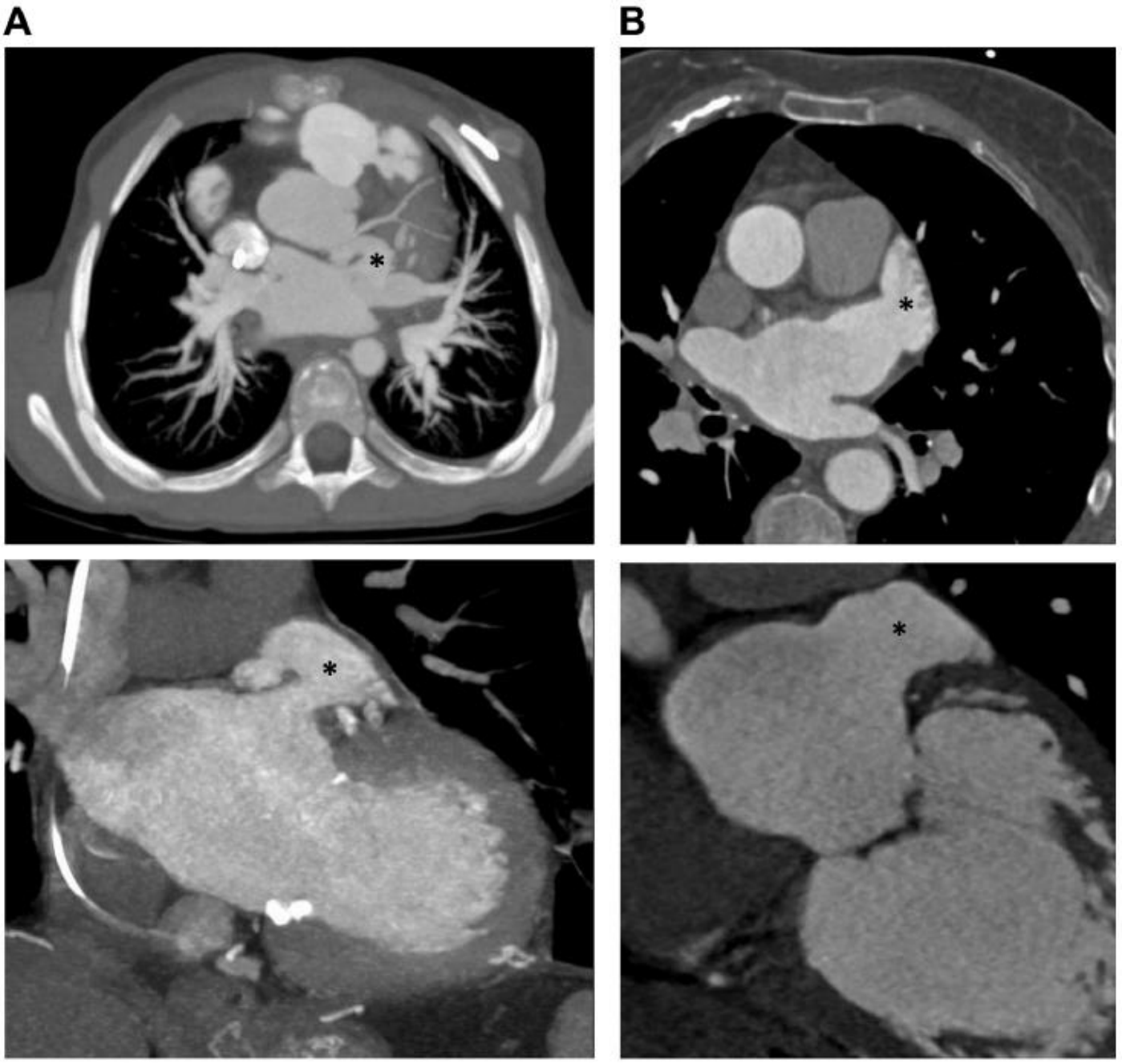
Thrombus in LA appendage of AF patient



- The shape of the LAA is variable.
- **4 main morphologies of LAA**

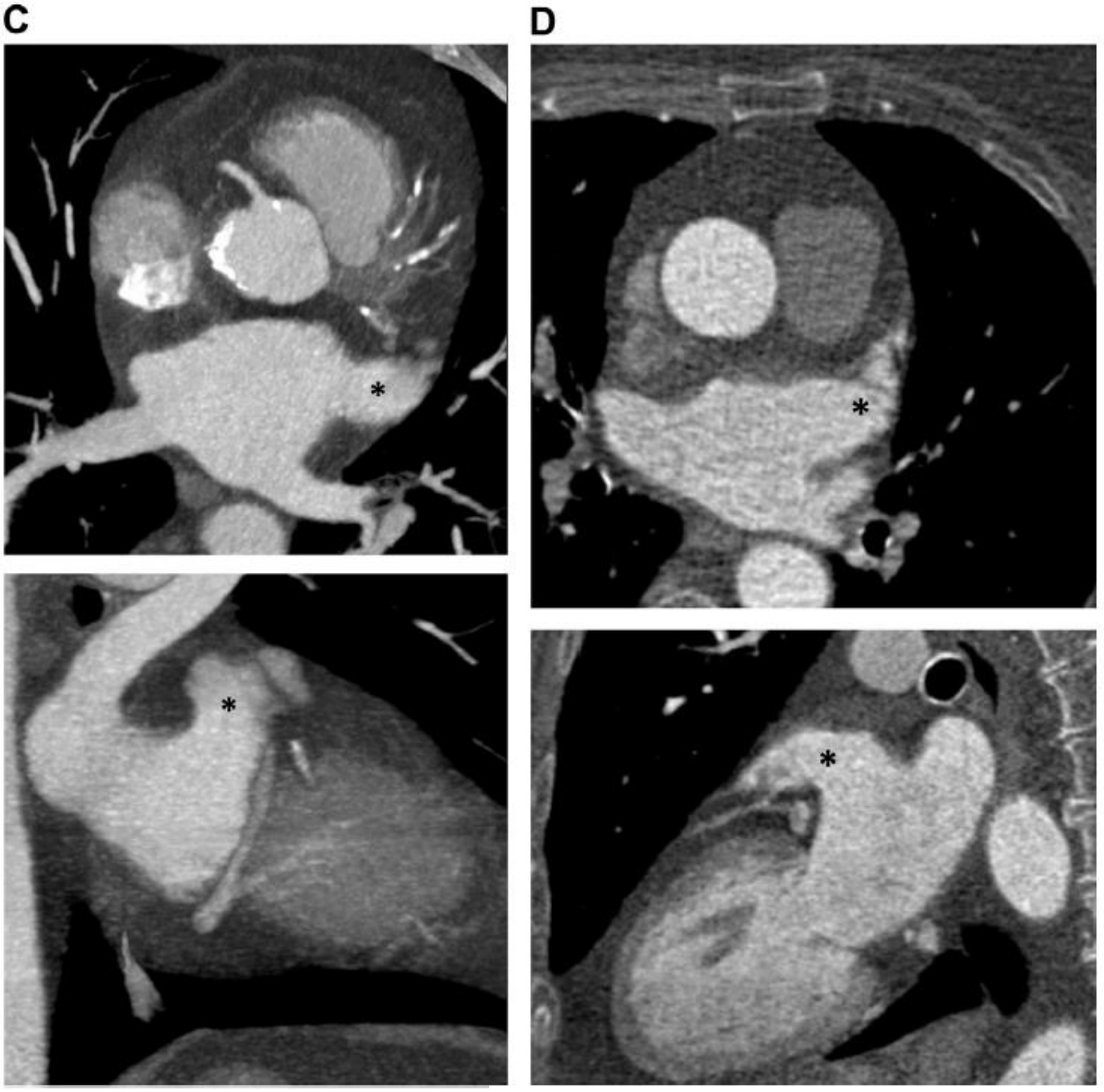
  : cactus, chicken wing, windsock, and cauliflower



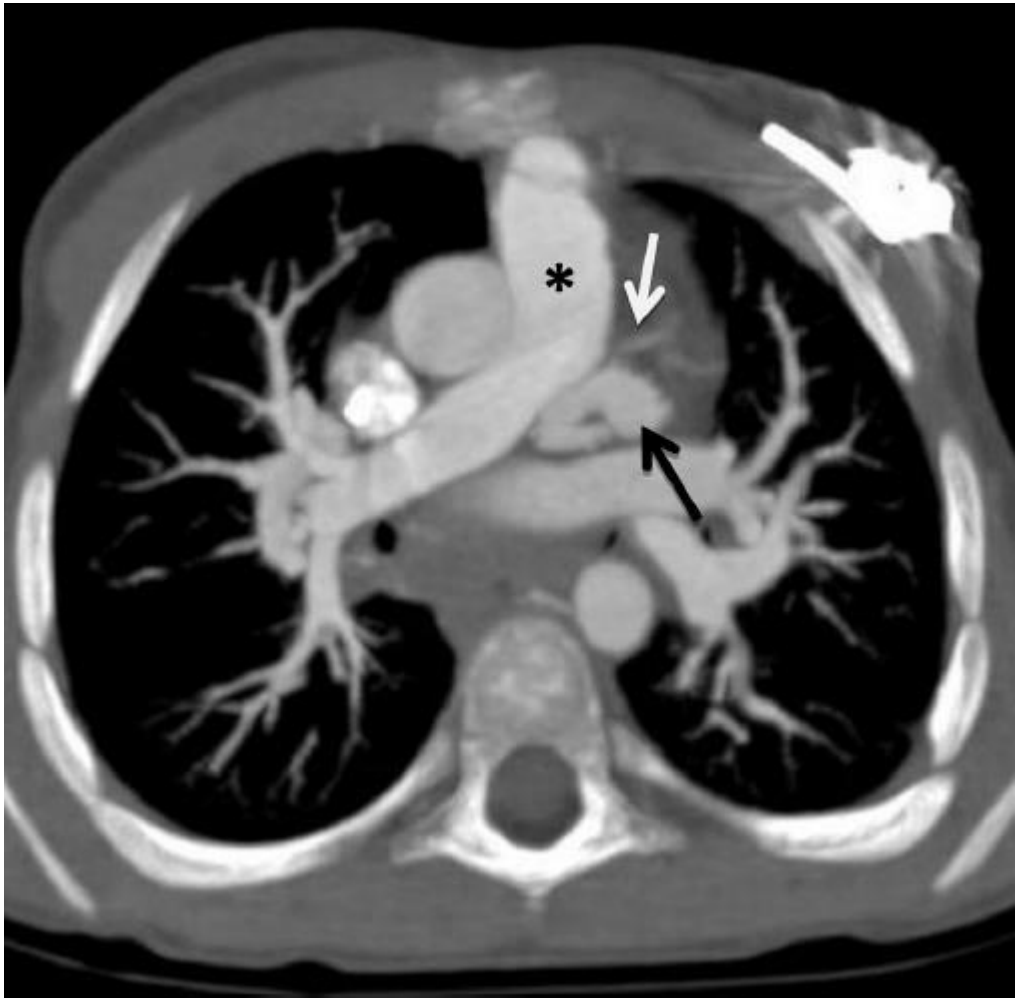


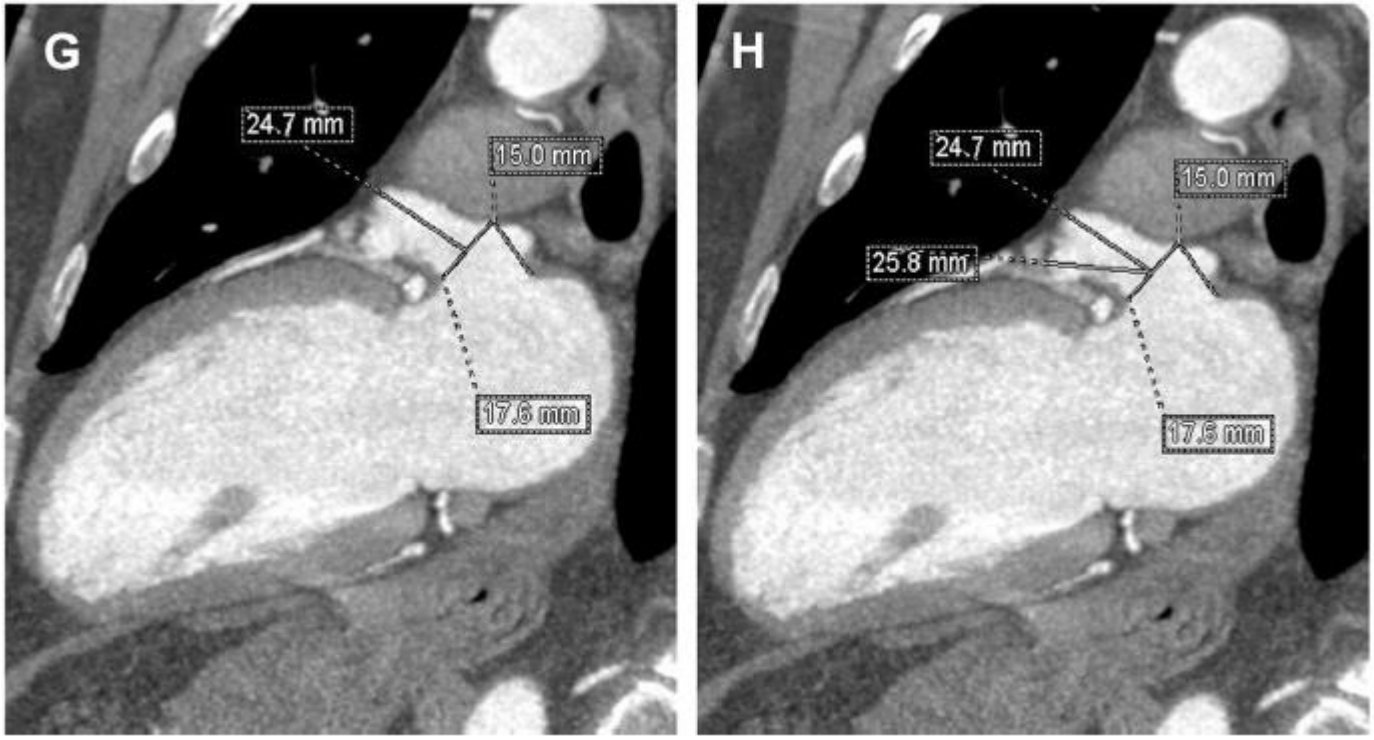
(A) chicken wing, (B) windsock,

Ismail TF, et al. J Cardiovasc Comput Tomogr. 2015



(C) cauliflower, and (D) cactus types *Ismail TF, et al. J Cardiovasc Comput Tomogr. 2015*

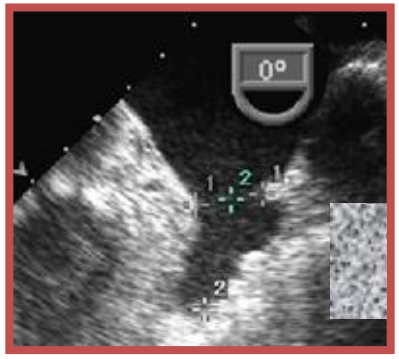




- The distance between the landing zone and the apex of the primary lobe
  : LAA length for Watchman device
- If the appendage is particularly angulated, there may be insufficient usable length to meet this requirement.

Ismail TF, et al. J Cardiovasc Comput Tomogr. 2015

Assessment of LAA



Measure LAA ostium in at least
4 TEE views

At 0 deg (from left coronary artery to a point 2 cm from tip of the LUPV limbus)

At 45, 90, 135 deg (from the top of the MV annulus to a point 2 cm from tip of the LUPV limbus)

Measure the approximate LAA useable length from the ostium line to the apex of the LAA

Transcatheter occlusion of the LAA

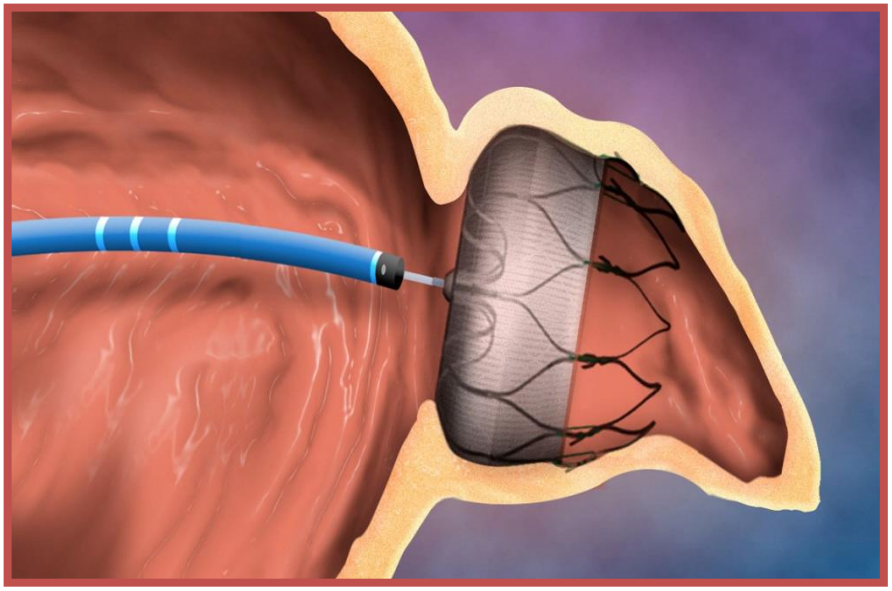
WATCHMAN®

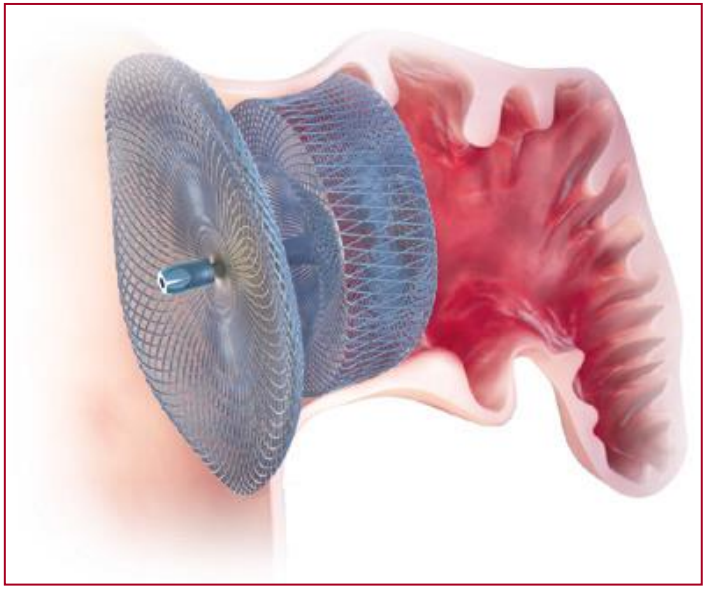
AMPLATZER Cardiac Plug

CE mark in 2008
not currently approved in the US

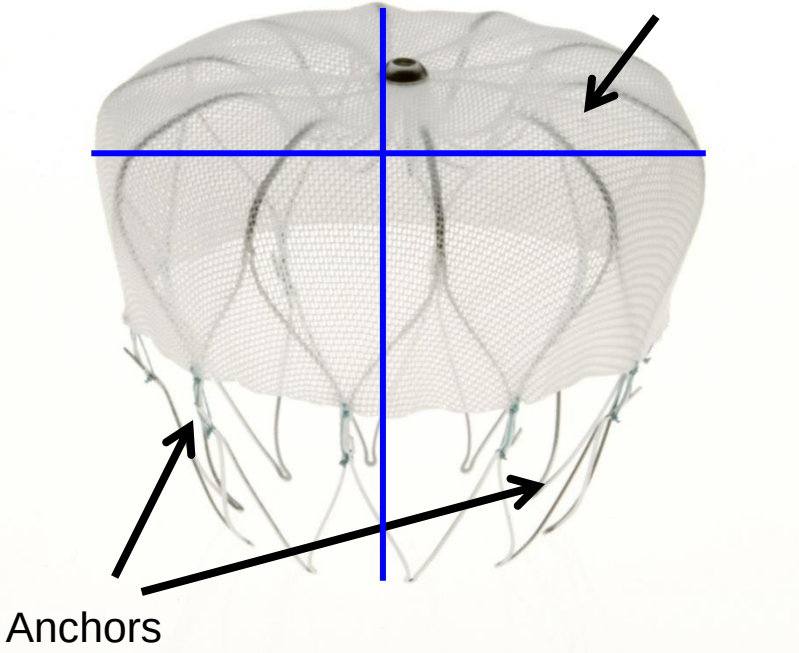
LAA Closure

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.





WATCHMAN Device



Nitinol Frame

- Radially expands to maintain position in LAA
- Available sizes:
  - 21, 24, 27, 30, 33 mm (diameter)
- 10 Active fixation anchors around device perimeter designed to engage LAA tissue for stability and retention
- Contour shape accommodates most LAA anatomies

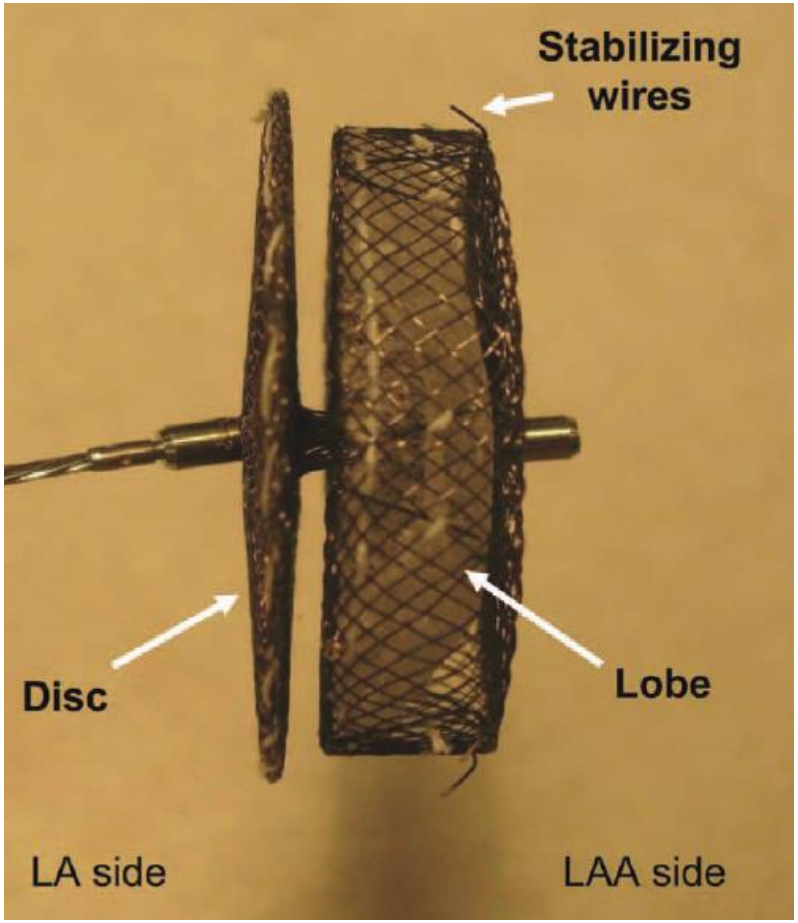
160 Micron Membrane

- Polyethylene terephthalate (PET) cap
- Designed to block emboli from exiting the LAA
- Intended to promote healing process

Length = Width of device

Advantage of length : stabilizing the device

AMPLATZER Cardiac Plug (ACP) Device



- Shallow device
- Disc 4~6 mm larger than lobe
- 8 sizes (lobe diameter from 16 to 30 mm)

- Ideal device for LAA with large ostium and shallow depth

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

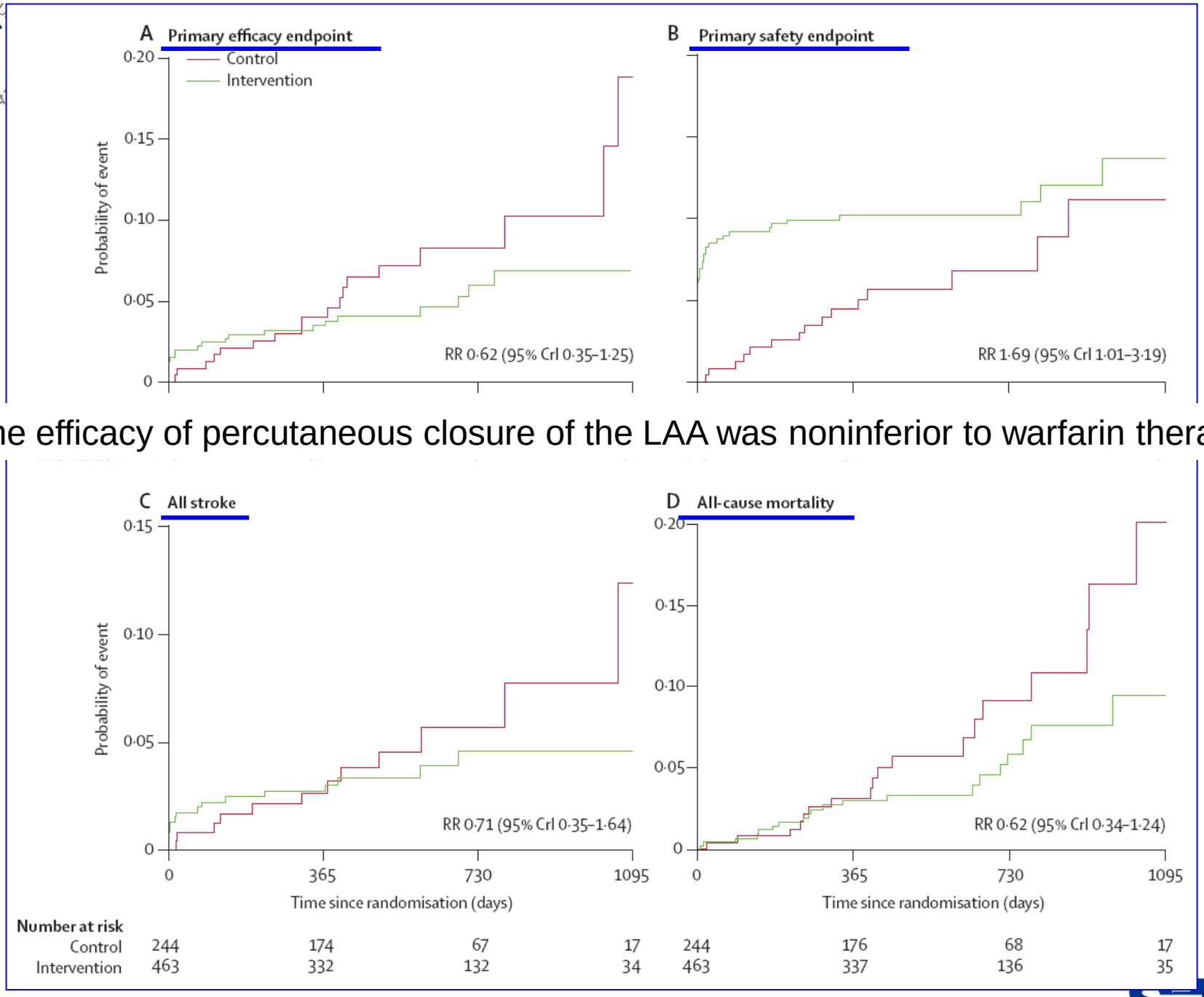
First prospective randomized clinical trial of LAA closure device

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 $\geq$ 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 $\geq$ 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
• Age >18 years, • **Nonvalvular AF** (paroxysmal, persistent, or permanent), • **CHADS2 score ≥ 1**,	• **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,



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

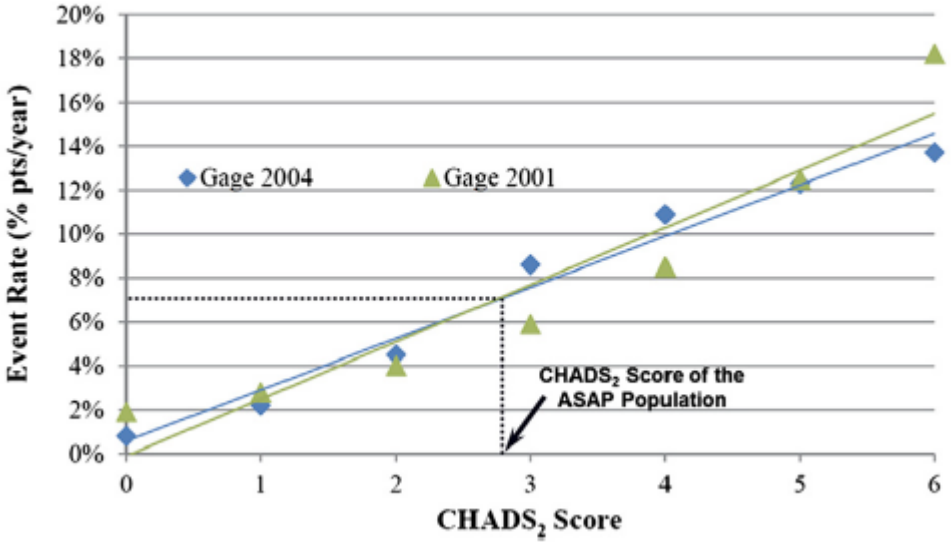
Holmes DR, et al. Lancet 2009; 374: 534

Watchman LAA closure in patients with a contraindication for anticoagulation (**ASAP study**)

- To assess the safety and efficacy of LAA closure in nonvalvular AF patients ineligible for warfarin

Inclusion criteria	Exclusion criteria
• Age >18 years, • Nonvalvular AF (paroxysmal, persistent, or permanent), • CHADS2 score ≥ 1, • **Contraindication** for even short-term oral **anticoagulation** therapy, • Eligibility for 6 months of treatment with a thienopyridine antiplatelet agent (clopidogrel or ticlopidine) and lifelong aspirin.	• **LVEF < 30%,** • Intracardiac thrombus/ dense spontaneous contrast by TEE, • Patent forman ovale with atrial septal aneurysm, • Complex atheroma with mobile plaque in the ascending aorta/aortic arch, • Significant mitral stenosis, • Existing pericardial effusion >3 mm • Recent MI within 3 mo • TIA/stroke within 30 days • Implanted mechanical valve prosthesis • Symptomatic carotid disease

Watchman LAA clo
contraindication for ant



Expected annual rate of stroke based on CHADS2 score

Clinical Outcomes

	Entire Events/Patient-Years
Primary efficacy	8/175.0 (4.6%)
Death, all cause	9/180.0 (5.0%)
All stroke	4/176.0 (2.3%)
Ischemic stroke	3/176.9 (1.7%)
Hemorrhagic stroke	1/179.1 (0.6%)

Procedure and device-related serious adverse events (N=150)

Device embolization	2 (1.3%)
Pericardial effusion with tamponade (percutaneous drainage)	2 (1.3%)
Femoral hematoma/bleeding	2 (1.3%)
Other†	3 (2.0%)
Total patients with procedure- and device-related SAEs	13 (8.7%)

WATCHMAN implantation without a warfarin transition might be safe and effective in AF patients with contraindications to oral anticoagulation

Reddy VY, et al. J Am Coll Cardiol 2013;61:2551

LAA closure with **Amplatzer Cardiac Plug** in patients with nonvalvular AF and contraIx to anticoagulation

- 52 patients in 7 Canadian centers
- Mean age 74 yrs, median CHADS2 score 3
- The procedure was successful in 98.1%
- Complications : device embolization (1.9%), pericardial effusion (1.9%)

Reasons for anticoagulation contraindication

Bleeding	
Intracranial hemorrhage	18 (34.6)
Gastrointestinal bleeding	12 (23.1)
Spontaneous hematoma of abdominal muscles	7 (13.5)
Otorhinolaryngological	4 (7.7)
Respiratory	3 (5.8)
Recurrent severe hematuria	1 (1.9)
Ophthalmological	1 (1.9)
Recurrent hemarthrosis	1 (1.9)
International normalized ratio lability	2 (3.8)
High risk of fall	1 (1.9)
Warfarin allergy	1 (1.9)
Severe anemia	1 (1.9)

90.4%

Urena M, et al. J Am Coll Cardiol 2013;62:96

Indication and patients selection for LAA closure

- ESC guidelines : percutaneous LAA closure

  “may be considered in patients with a **high stroke risk** and **contraindications for long-term oral anticoagulation**”.

The level of evidence is “B”.

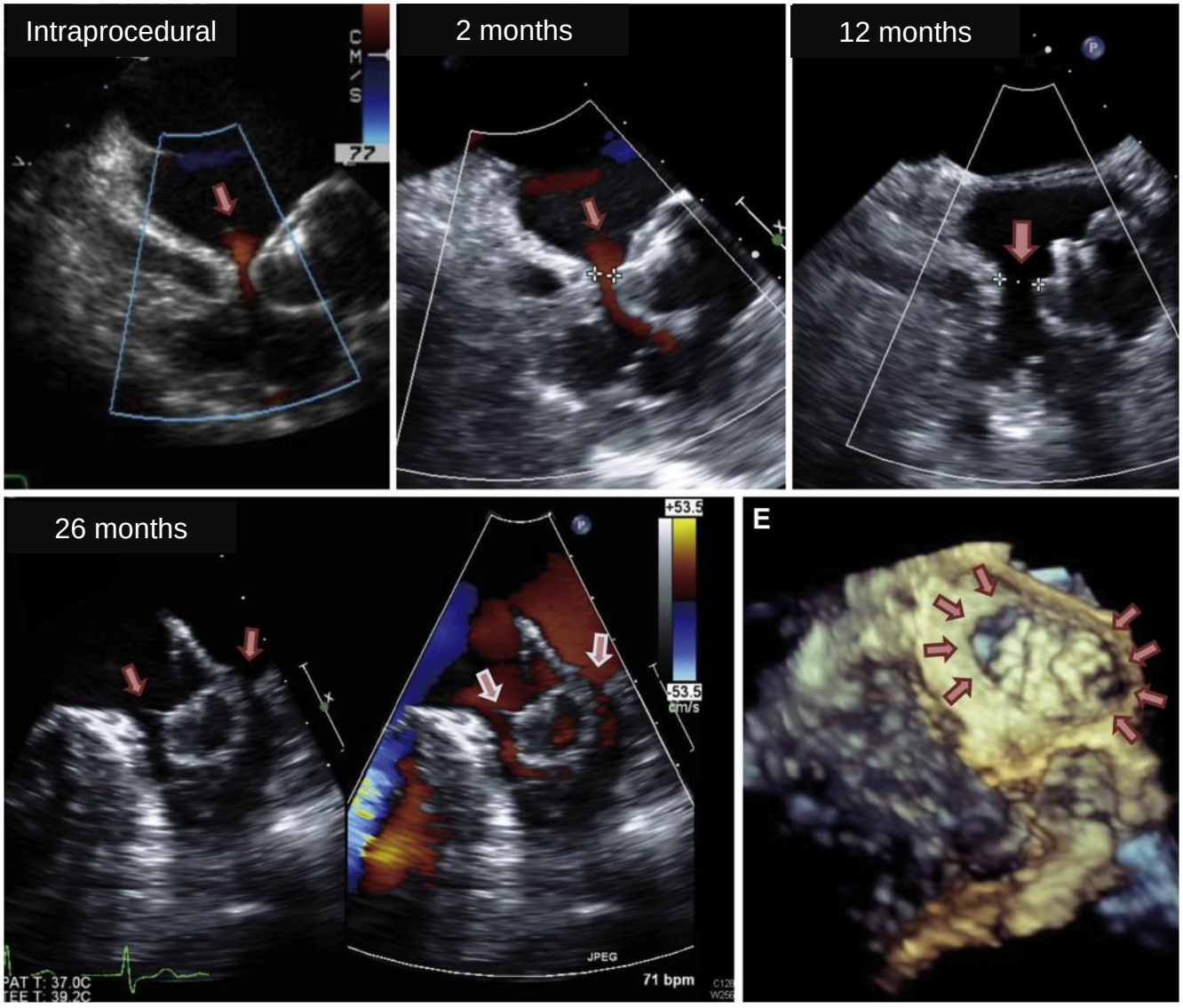
Recommendations	Class[a]	Level[b]
Interventional, percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation.	IIb	B
Surgical excision of the LAA may be considered in patients undergoing open heart surgery.	IIb	C

ESC 2012 AF guidelines

Limitation of LAA closure

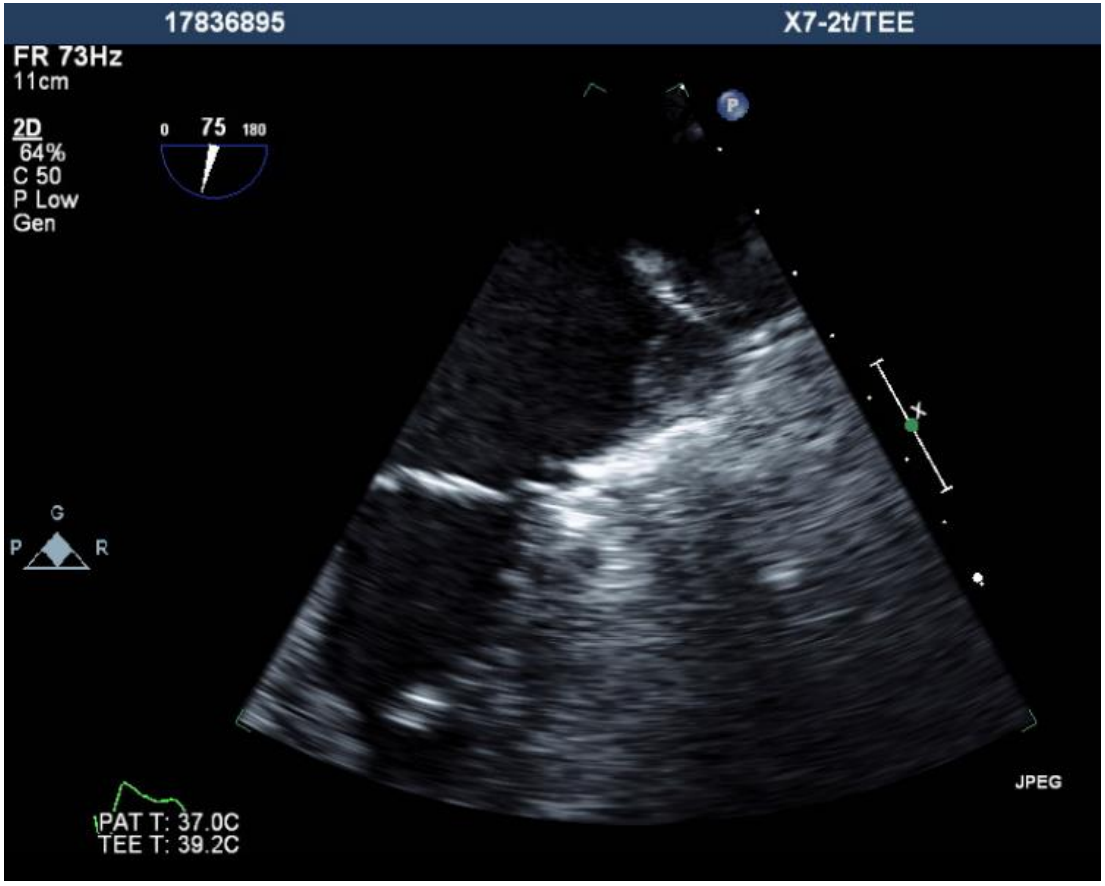
- **The source for stroke in AF patients**
  In theory, LAA closure only is **not** sufficient to effectively prevent the occurrence of thromboembolic events
  : a smaller proportion of **thrombi** were located **outside the appendage**
- **Residual peri-device leakage** after LAA closure in about 1/3 patients
- **Device-associated thrombus** was reported even after complete endothelialization of the device.
- **Antithrombotic therapy after LAA closure**
  : the choice of antithrombotic drugs
  and the time of antithrombotic therapy
- Era of new oral anticoagulants (**NOACs**)
- Lack of **long-term efficacy and safety**
- **Economic evaluation**

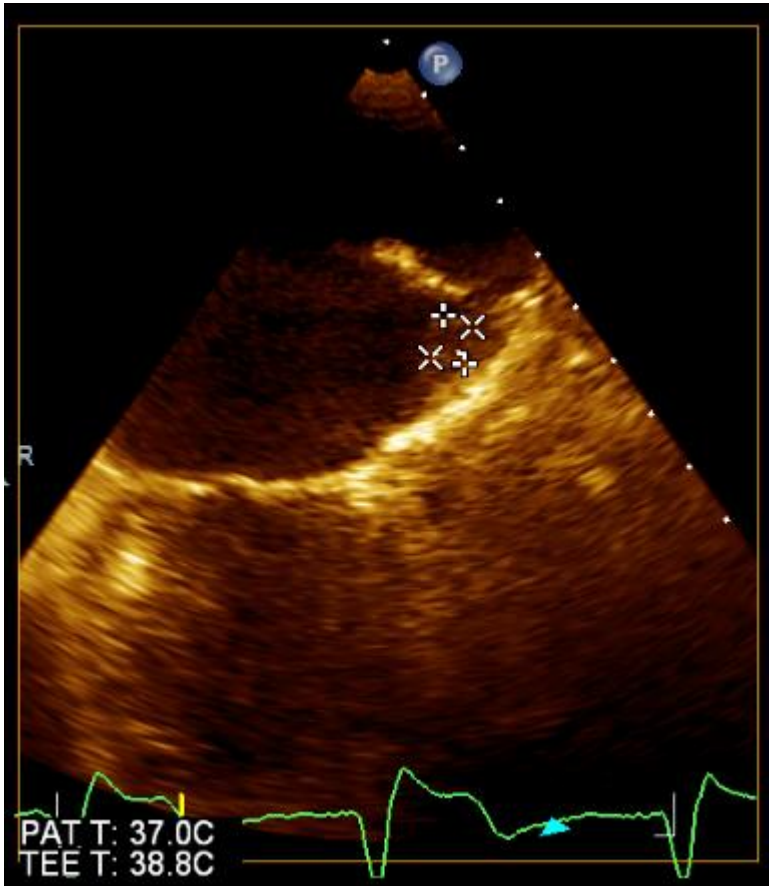
A case with progressive increase in peridevice leakage after the Implantation of the Watchman device



Lee K, et al. Can J Cardiol 2014;30(11):1461

Thrombus below a tip of ACP : 1 year 3 months after implantation





FDA Circulatory System Devices Panel Meetings on WATCHMAN LAA Closure Therapy

- The WATCHMAN LAAC device is indicated
  to prevent thromboembolism from the left atrial appendage.
- The device may be considered for patients with nonvalvular AF who, based on **$CHADS_2$** or **CHA_2DS_2-VASc** scores, would be recommended for warfarin therapy to reduce the risk of stroke and systemic embolism.

- The device has a role in a specific group of patients, suggesting that the device would be used as a **second-line therapy for appropriate patients.**

- The panel voted
  12 to 0 that the **WATCHMAN LAA closure device is safe**;
  6 to 7 that it is not effective;
  and **6 to 5**, with 1 abstention, that its benefits outweigh its risks.

Waksman R, et al. Am J Cardiol 2015;115:378

Indication and patients selection for LAA closure

- **Non-valvular AF patients** who are eligible for long-term warfarin therapy for prevention of thromboembolism and eligible to come off warfarin therapy if LAA is sealed (**PROTECT-AF**)
- **Non-valvular AF patients** at high risk of stroke for whom effective conventional anticoagulant therapy is **not** available or presenting problems in managing the drug treatment (**ASAP**)

Potential patients for LAA closure

- **Non-valvular AF** patients who are **high risk of thromboembolism and high bleeding risk**
  - ✓ Recurrent bleeding on anticoagulation therapy
  - ✓ Contraindication to anticoagulation therapy
  - ✓ Intolerant to anticoagulation therapy
- **Non-valvular AF** patients who are **high risk of thromboembolism but no effective anticoagulation**
  - ✓ Prior stroke/TIA while on anticoagulation therapy
  - ✓ Persistent non-compliance to anticoagulation therapy
  - ✓ Unwilling to take anticoagulation therapy

Camm AJ, et al. Heart Rhythm 2014;11:514

Conclusions

- Non-pharmacologic **LAA closure** (Watchman, ACP device)
  :another option for prevention of stroke in selected AF patients
- **Non-valvular AF** patients who are **high risk of thromboembolism and high bleeding risk**
- **Non-valvular AF** patients who are **high risk of thromboembolism but no effective anticoagulation**