



PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA

Centro Congressi
di Confindustria

**Auditorium
della Tecnica**

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2022



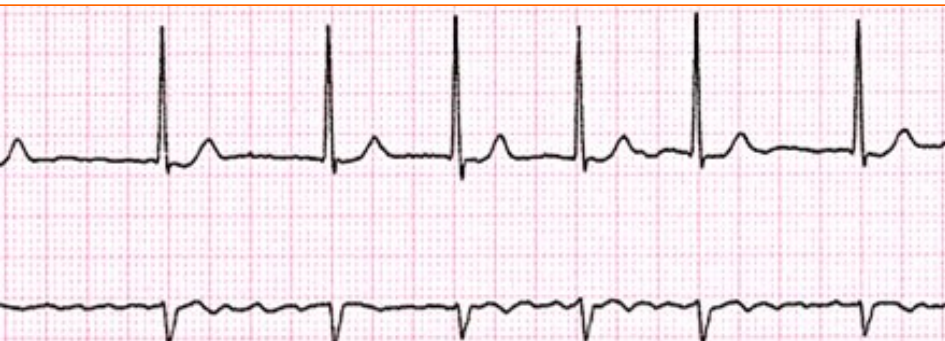
Aritmologia Clinica e Interventistica

Trombosi auricolare: quali anticoagulanti?

Vito Maurizio Parato, MD, FESC, FACC
San Benedetto del Tronto, Marche, IT



DISCLOSURE: None



NVAF is

- epidemiologically the most common arrhythmia..
- responsible of **15-20%** of all **ischemic strokes**..
- ☾ and 26% of all embolic events..

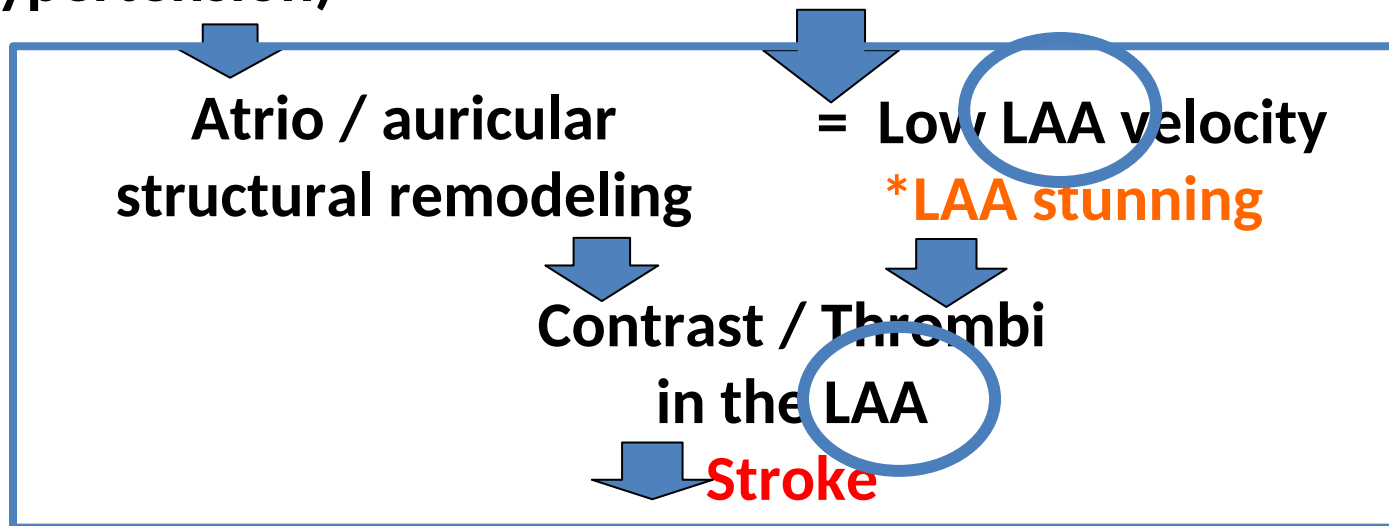
ESC, GLs

Stroke Patho-Physiology in NVAF

Patho-physiologic Cascade:

**Clinical Risk Factors (age
+ hypertension)**

**Long lasting AF or
Frequent / long PAF**



*Khan, Int J Card 2003
De Luca, Int J Card 2005
Colonna, JCM 2006*



European Heart Journal Advance Access published April 26, 2016



European Heart Journal
doi:10.1093/eurheartj/ehw159

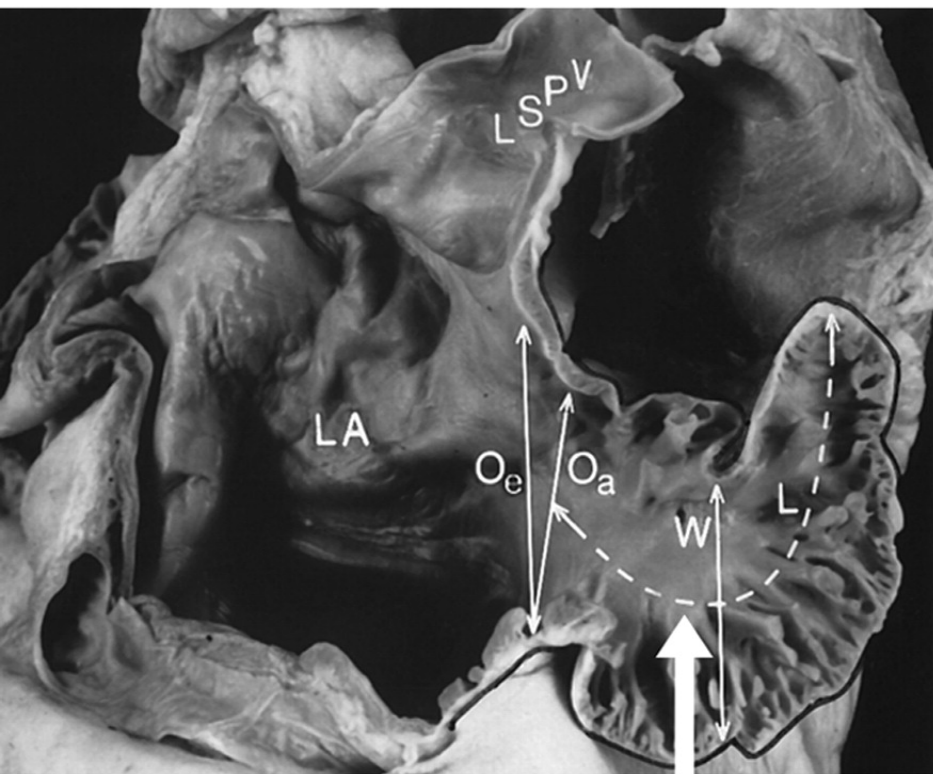
REVIEW

Clinical update

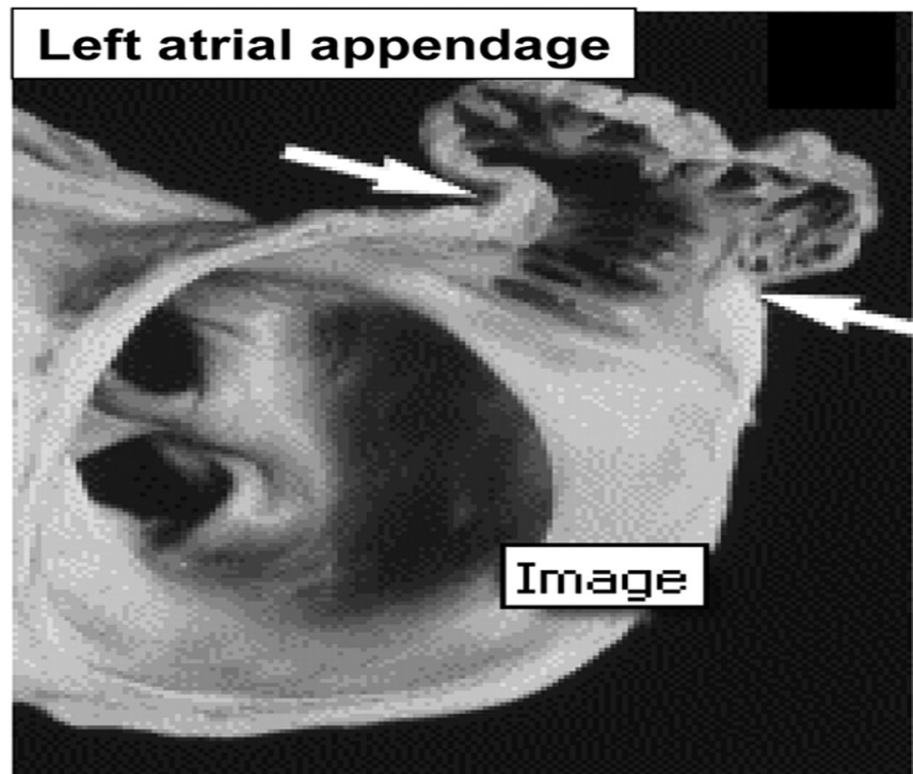


The left atrial appendage: from embryology to prevention of thromboembolism

Giuseppe Patti^{1*}, Vittorio Pengo², Rossella Marcucci³, Plinio Cirillo⁴, Giulia Renda⁵, Francesca Santilli⁶, Paolo Calabrò⁷, Alberto Ranieri De Caterina^{5,8}, Ilaria Cavallari¹, Elisabetta Ricottini¹, Vito Maurizio Parato^{9,10}, Giacomo Zoppellaro², Giuseppe Di Gioia¹, Pietro Sedati¹, Vincenzo Cicchitti⁹, Giovanni Davì⁶, Enrica Golia⁷, Ivana Pariggiano⁷, Paola Simeone⁶, Rosanna Abbate³, Domenico Prisco³, Marco Zimarino⁵, Francesco Sofi^{3,11}, Felicita Andreotti¹², and Raffaele De Caterina,
on behalf of the Working Group of Thrombosis of the Italian Society of Cardiology



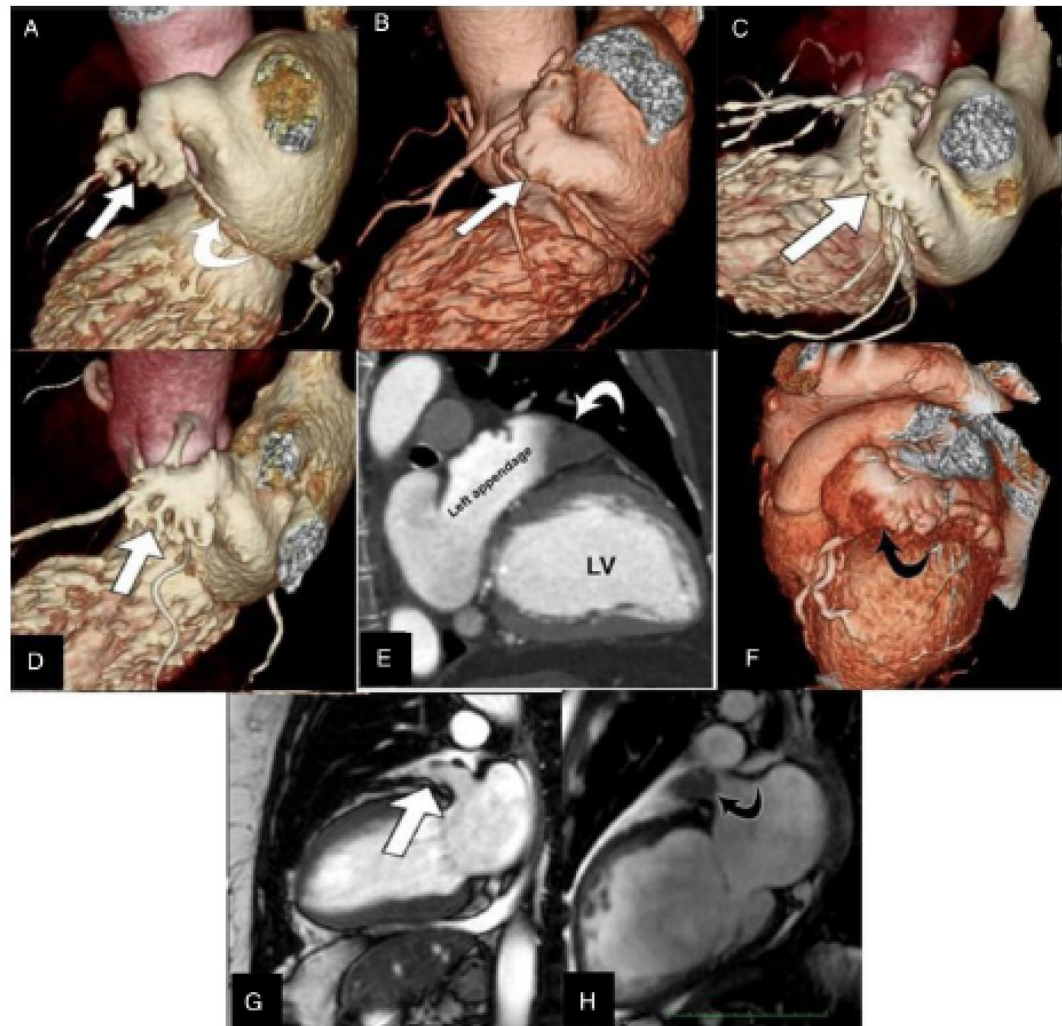
Left atrial appendage

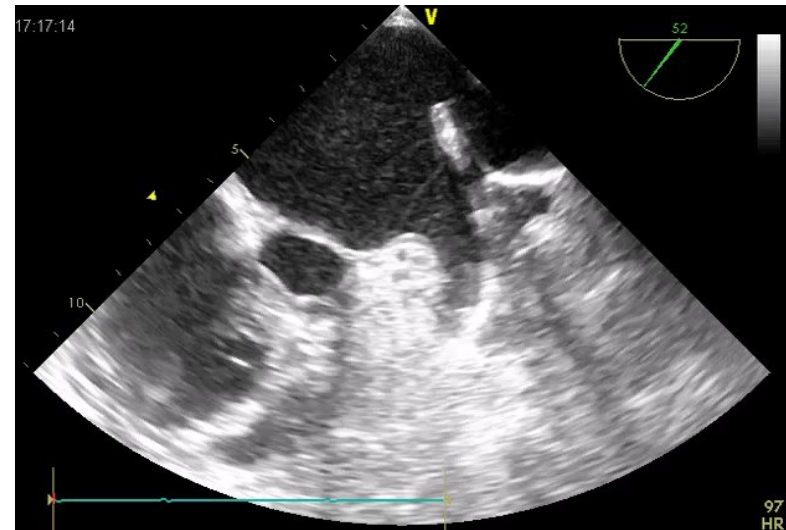


Left atrial appendage

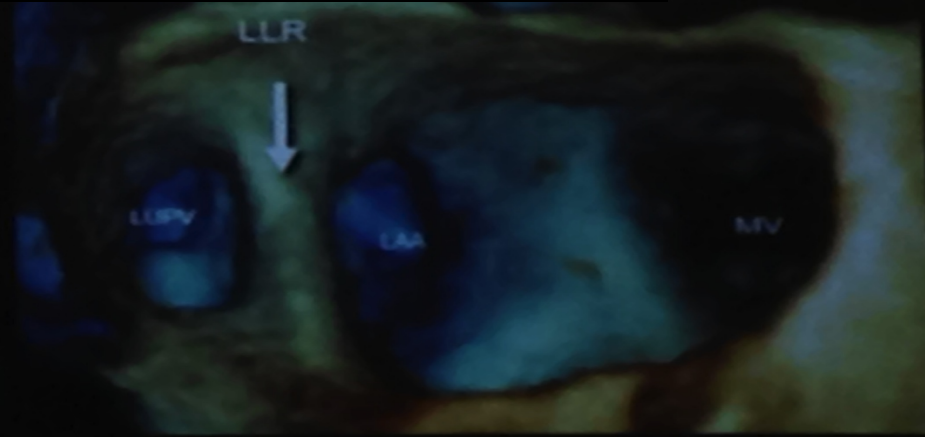
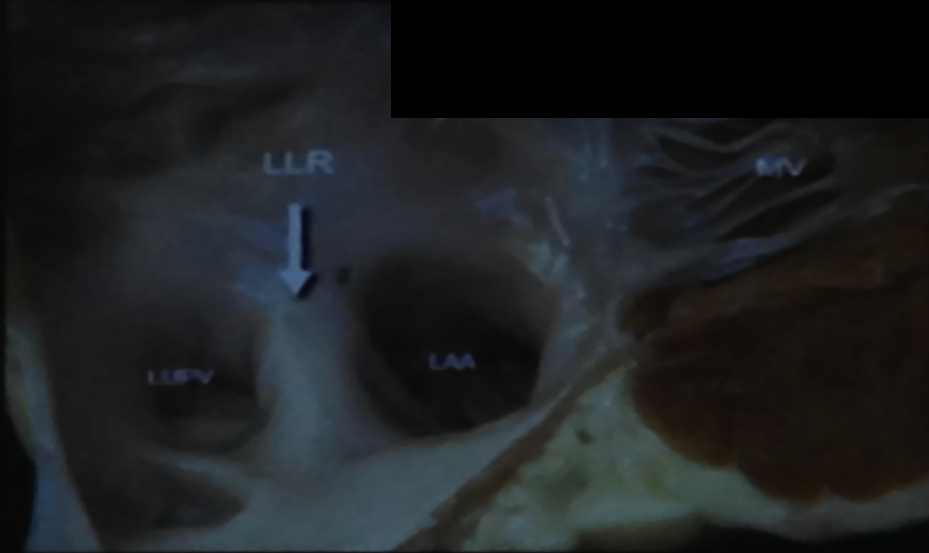
CT, MRI

Patti G, Eur H J, 2016





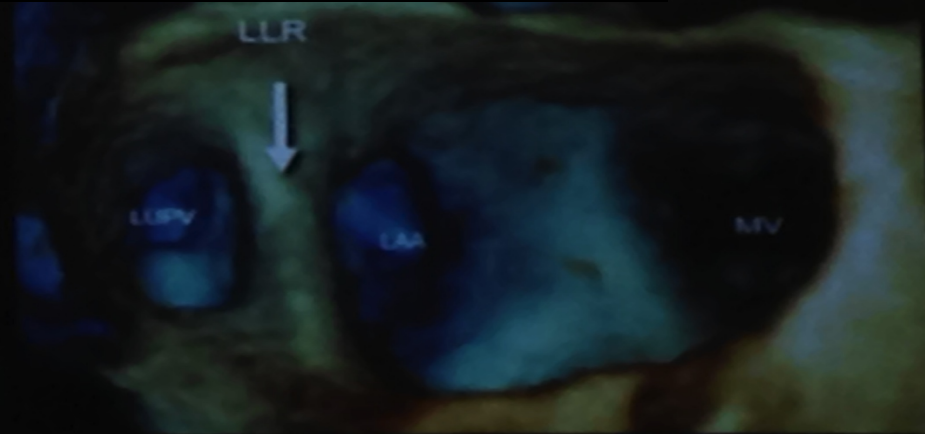
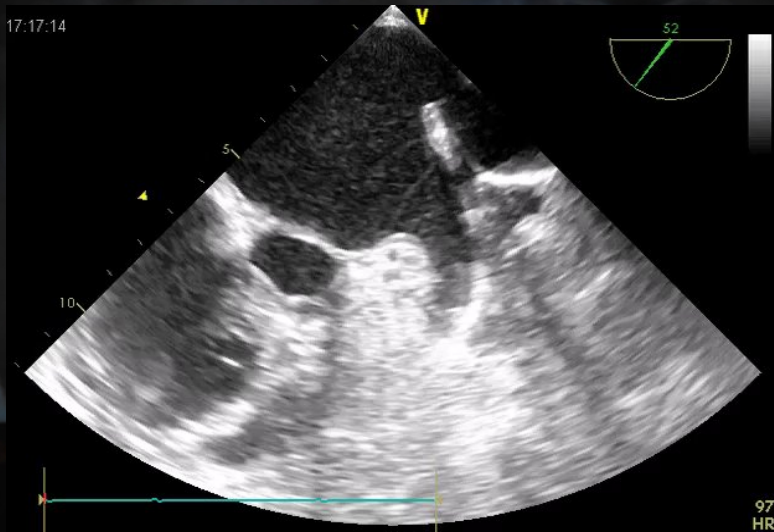
Marshall's Left Lateral Ridge (LLR)



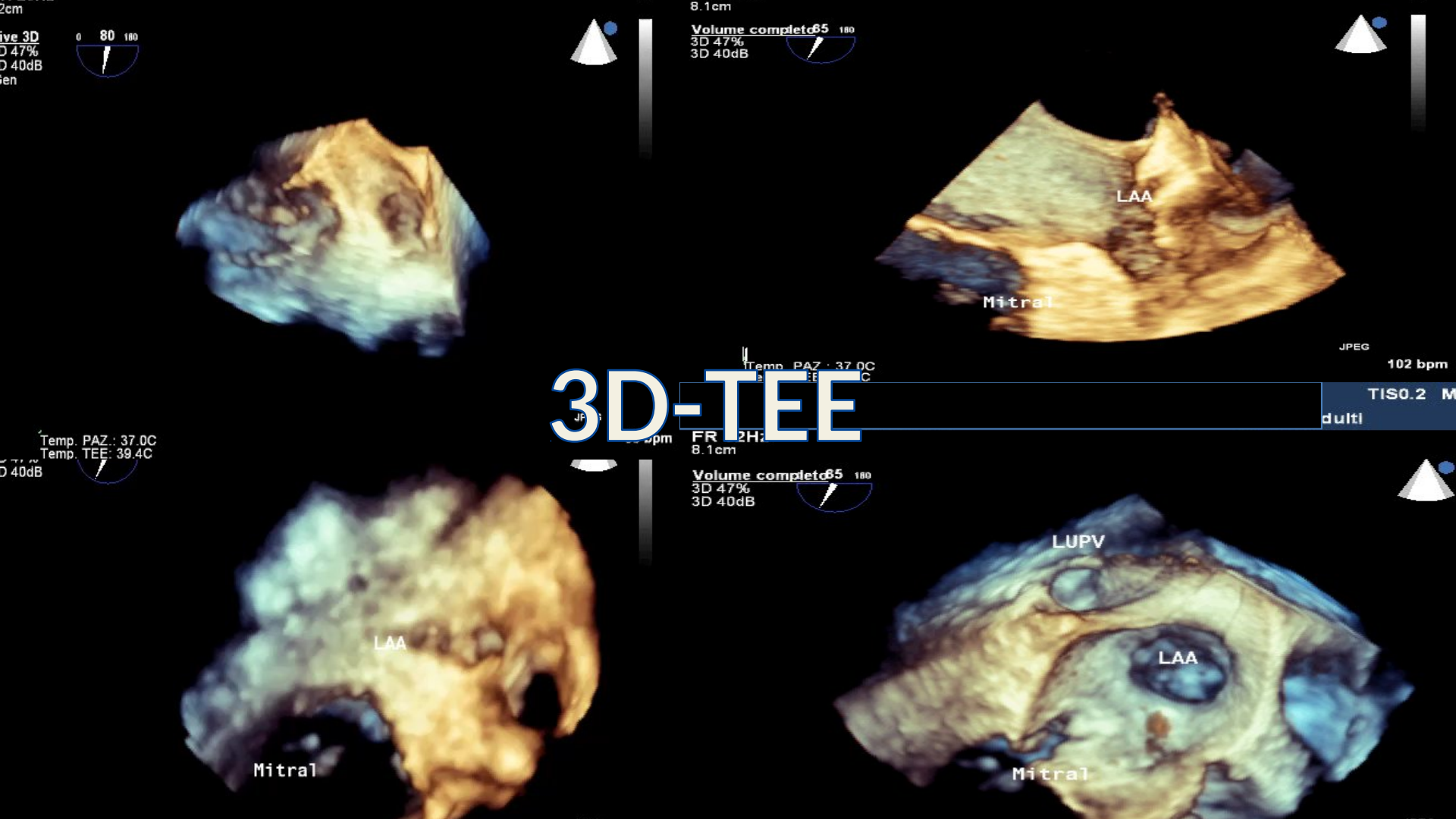
Saw Yan HO Royal Brompton Hospital

TEE-3D

Marshall's Left Lateral Ridge (LLR)



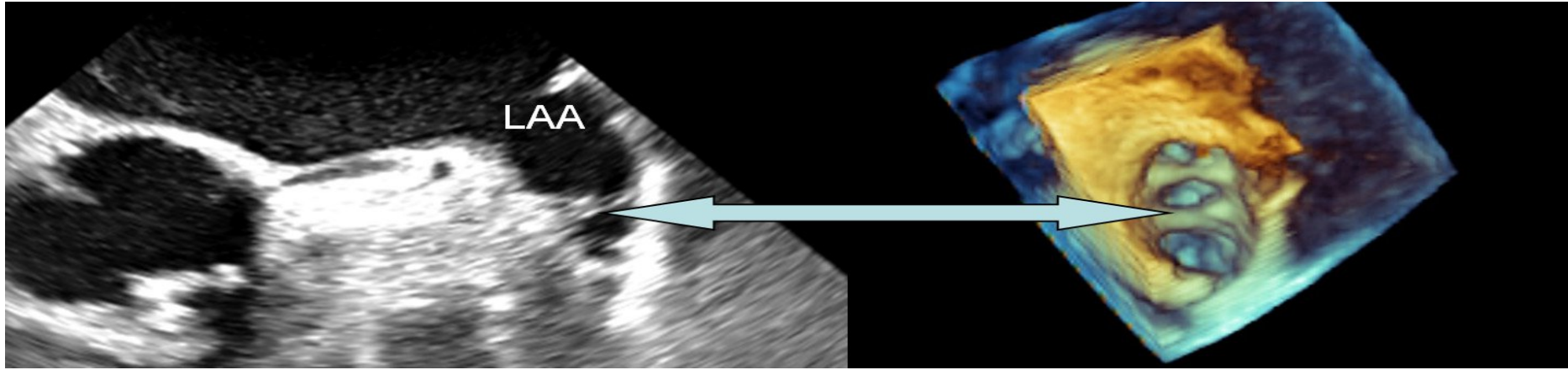
TEE-3D



LEFT ATRIAL APPENDAGE 3D ECHO: CLINICAL VALUE

Compared to 2D-TEE

- Better discrimination between pectinate muscles and thrombus..



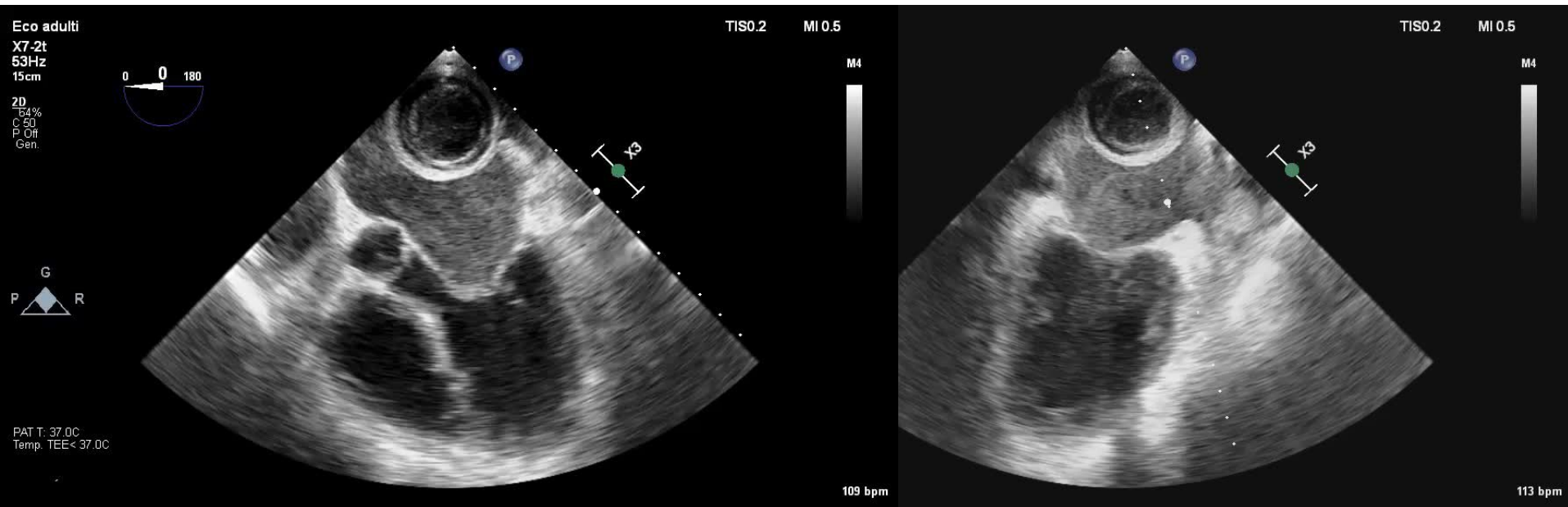


LA/LAA

AF-induced pathology

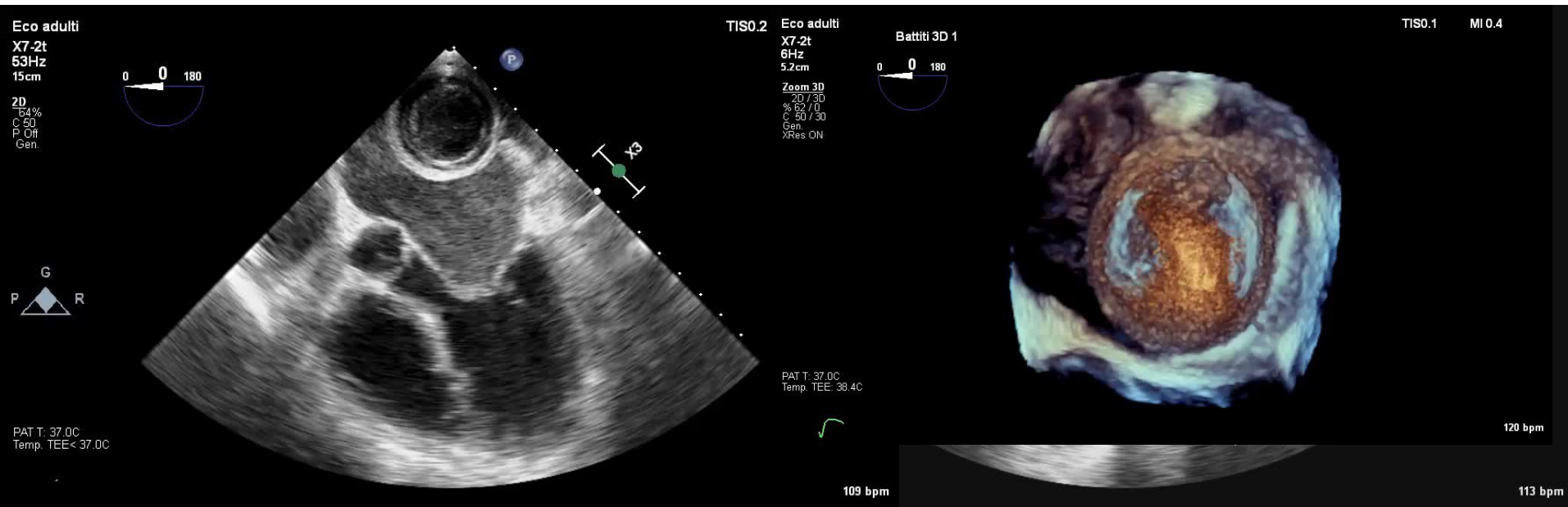


Valvular AF – Mitral Stenosis





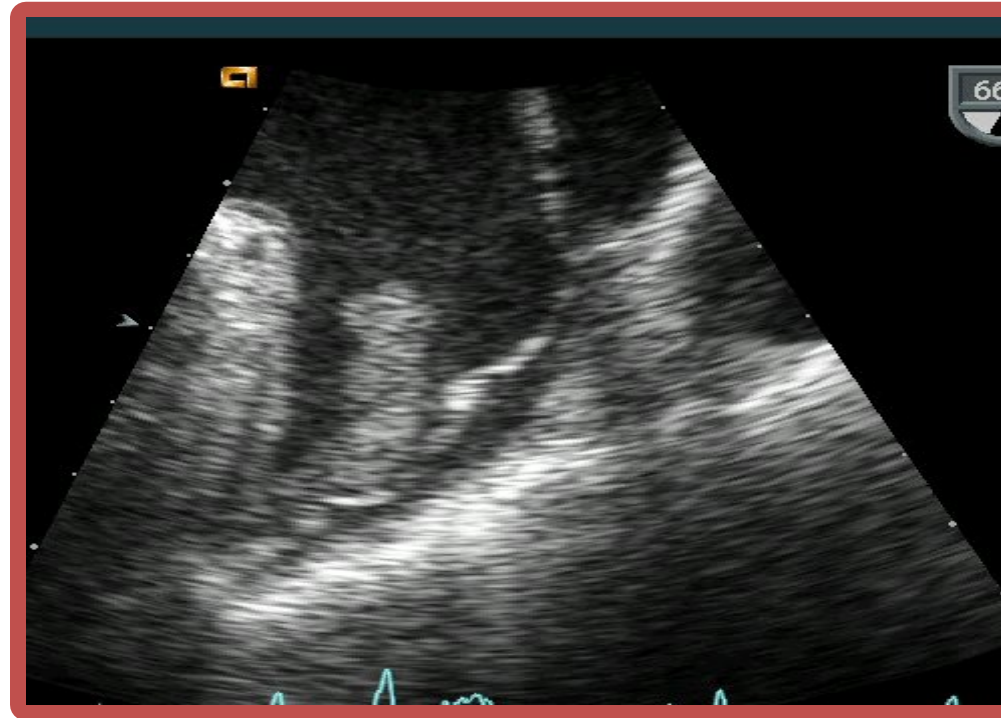
Valvular AF – Mitral Stenosis



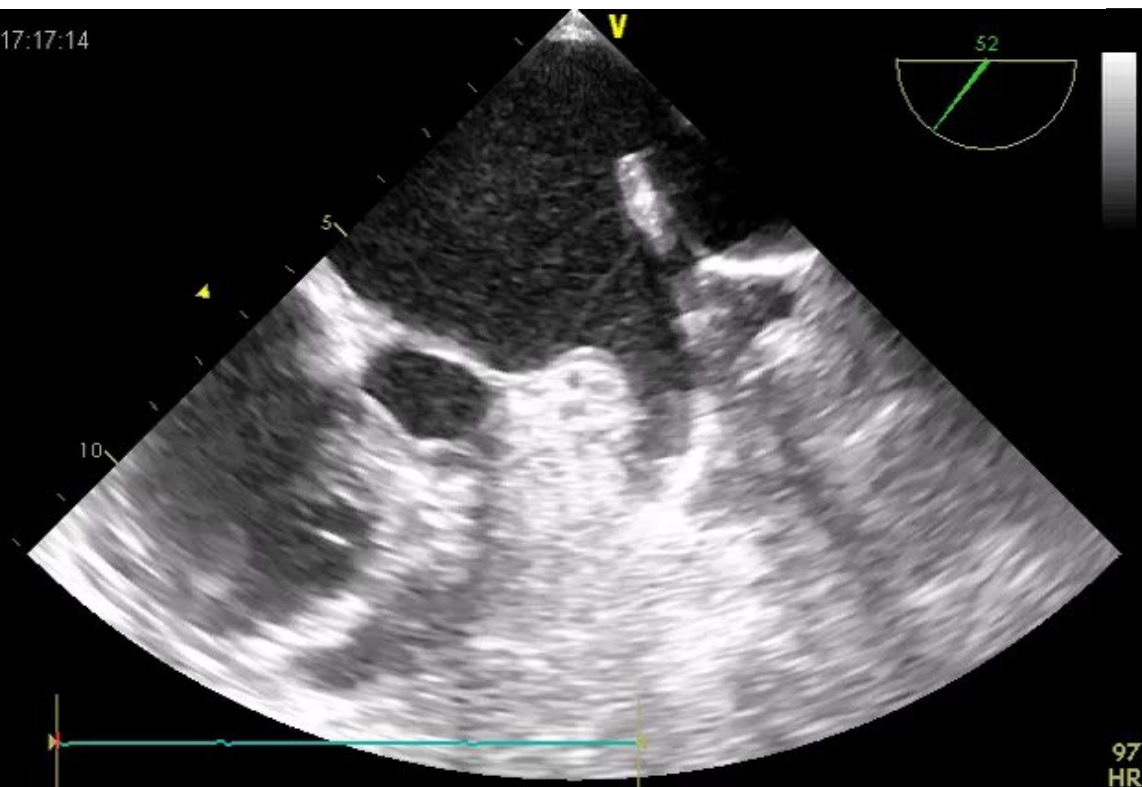
NVAF – LAA/Thrombosis



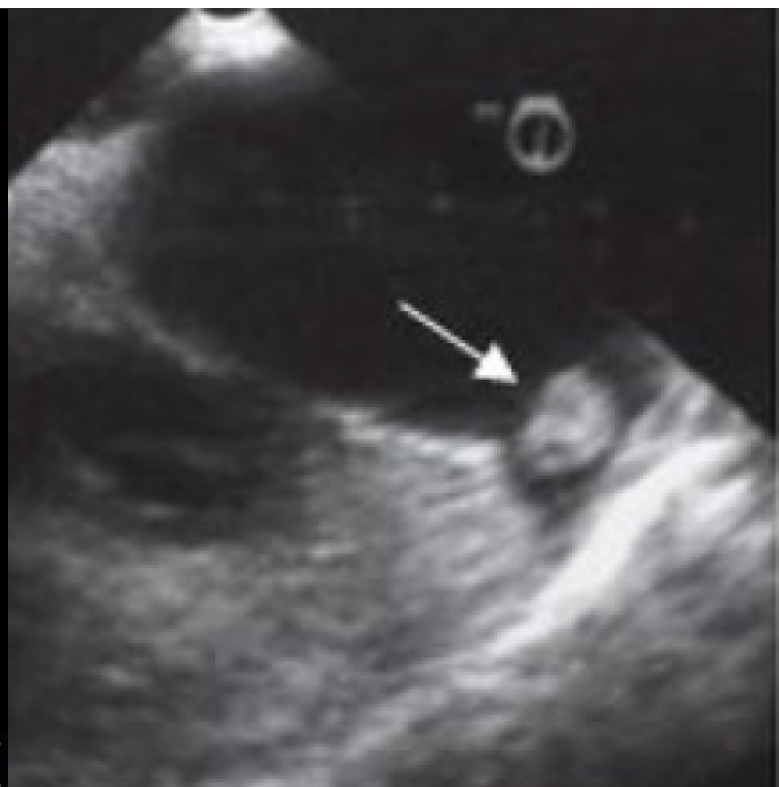
Soft Ovaloid



Soft Elongated



Dense Echocontrast

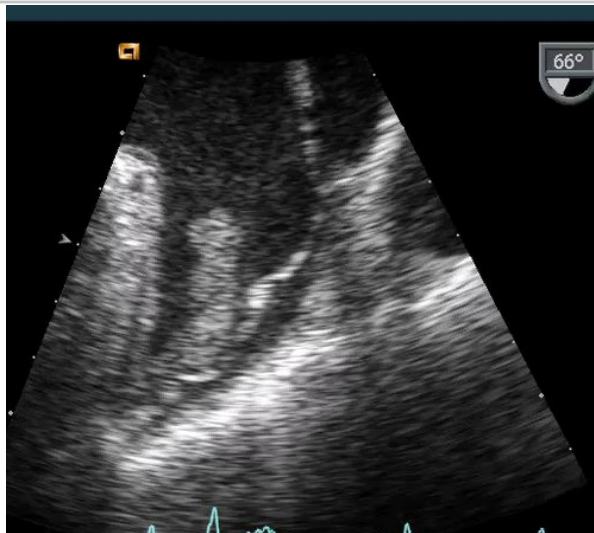


Calcified

LAA-Thrombus Formation

- Blood stasis
- Endotelial Dysfunction
- Hypercoagulable status

Virchow's triad



LAA Thrombus in NVAF

..begins to form after the onset of AF and it requires ≥ 3 days to form..

LAA-Thrombi (THR) in NVAF= **6-18%** (9.3%)

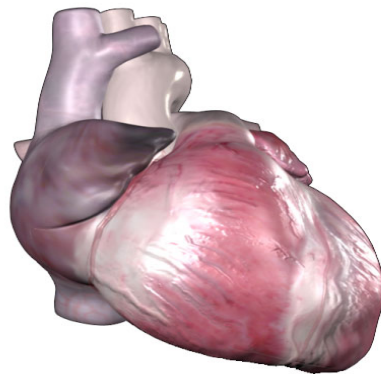
Incidence (317 pts):

- 14% in acute AF (<3 days)
- 27% in chronic AF

Frequency and significance of **right** atrial appendage thrombi in patients with persistent atrial fibrillation or atrial flutter

No. 983 pts with AF/AFL

- LAA-THR= 9,3%
- RAA-THR= 0.73%



Cresti A, JASE 2014;27

Echocardiography in AF: information for clinical decisions

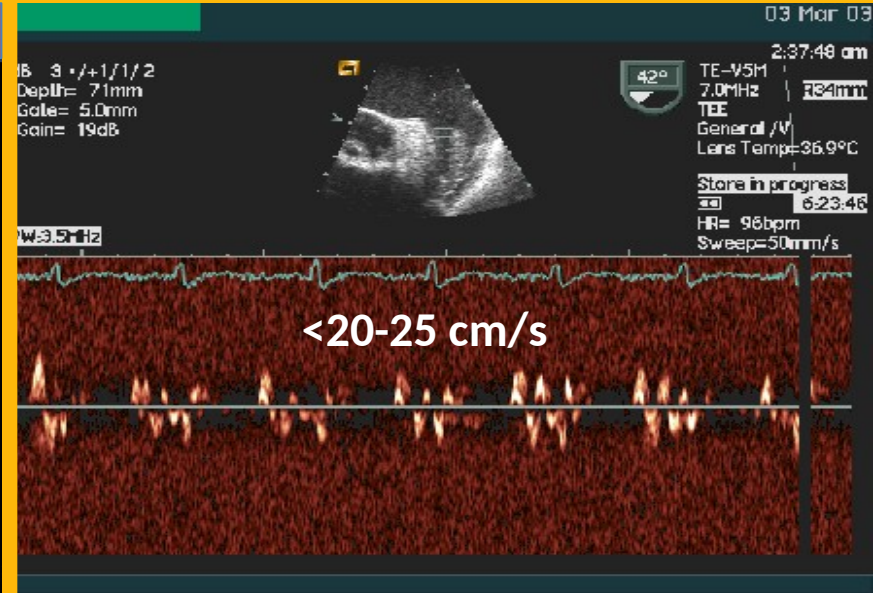
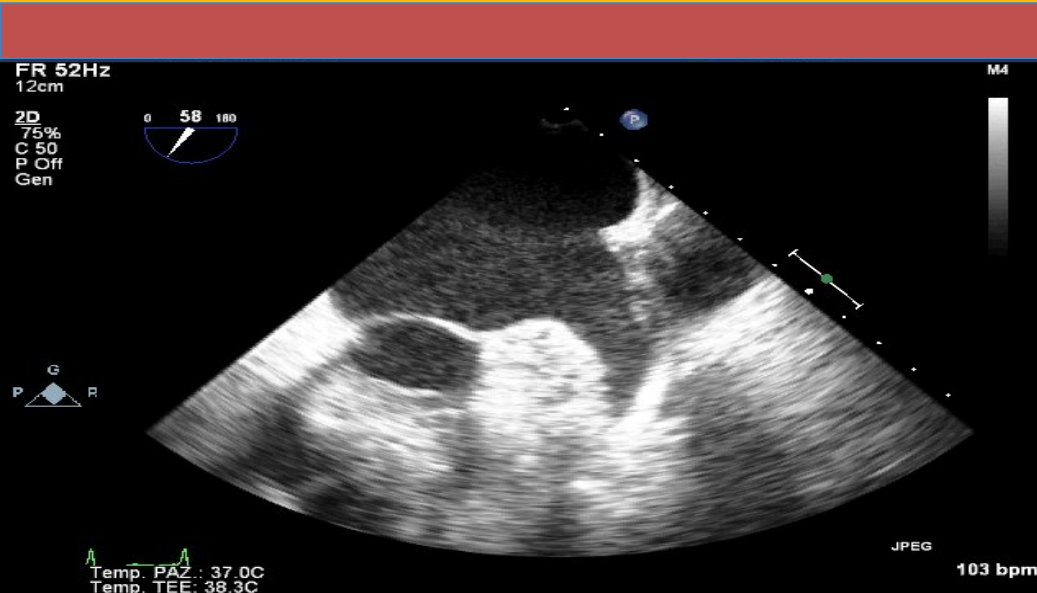
EAE recommendations, EJE 2010

- Thrombi
- Spontaneous Echo-Contrast
- LAA Emptying Velocities
- **LV function and thrombi**
- Patent Foramen Ovale
- Complex Aortic Plaques



Atrio-Auricular
function

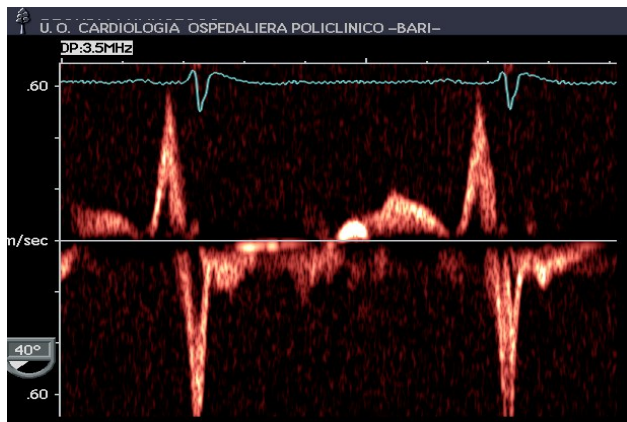




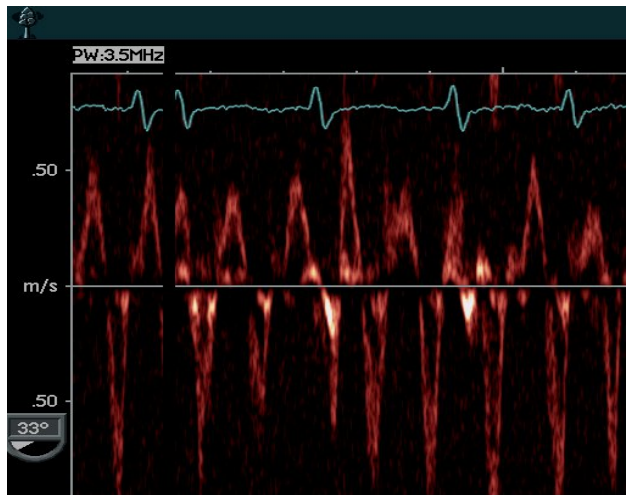
Left Atrial Appendage Dysfunction

Normofunctioning LAA

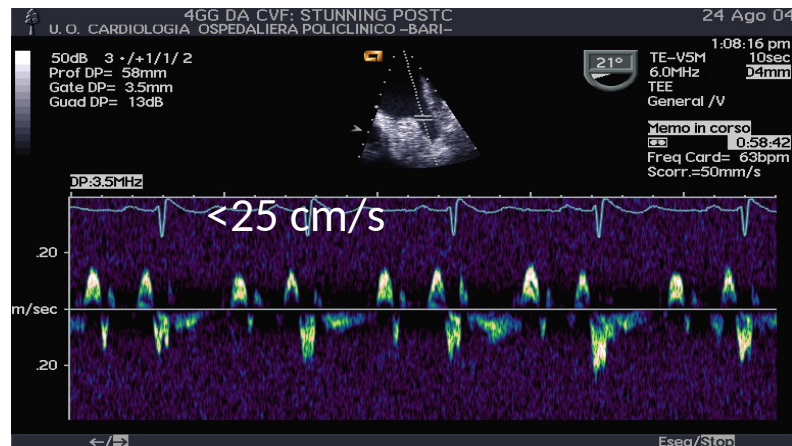
SR



AF

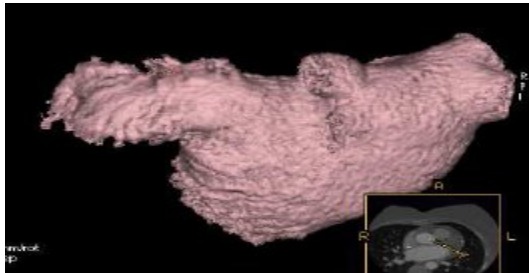
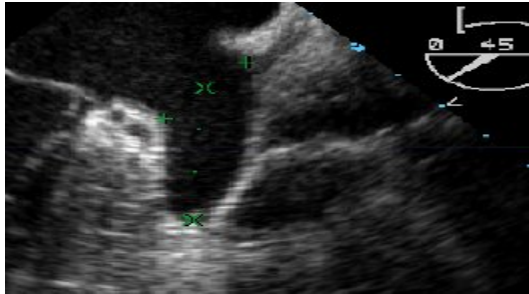


Dysfunctioning LAA

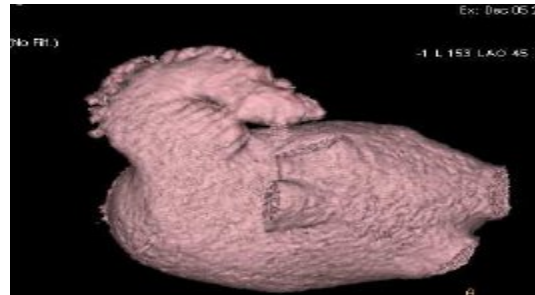
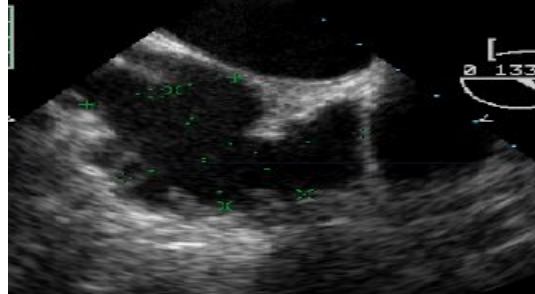


LAA Common Morphologies

The Wind Sock Type



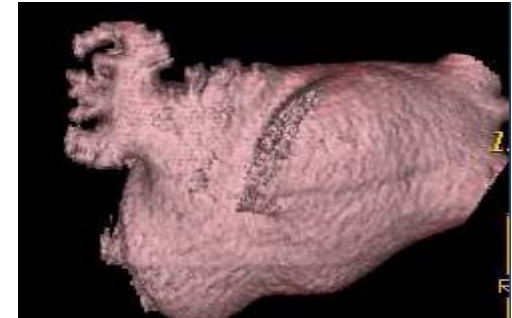
The Chicken Wing Type



The Broccoli Type



Di Biase L, JACC 2012

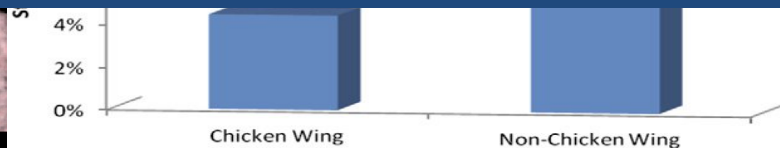


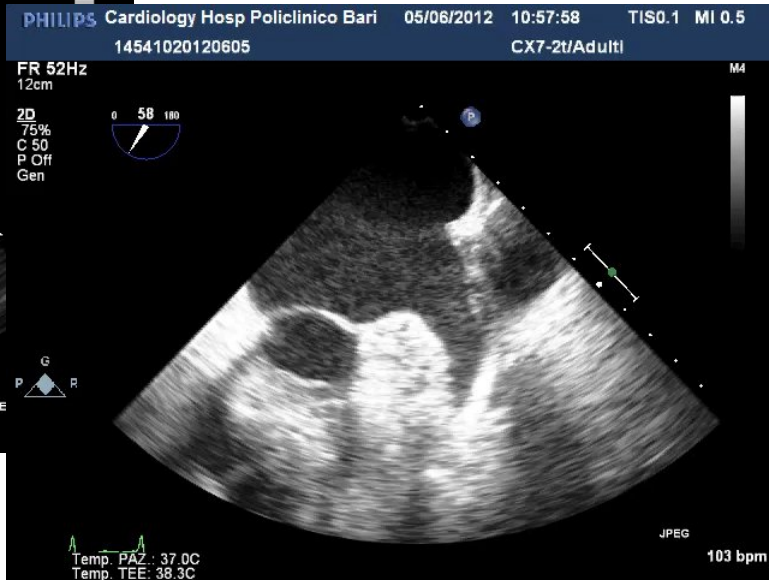
Does the left atrial appendage morphology correlate with the risk of stroke in patients with AF?

Di Biase L et al, JACC 2012

..superior LAA takeoff (higher than that of the left superior pulmonary vein)= **higher T-E risk..**

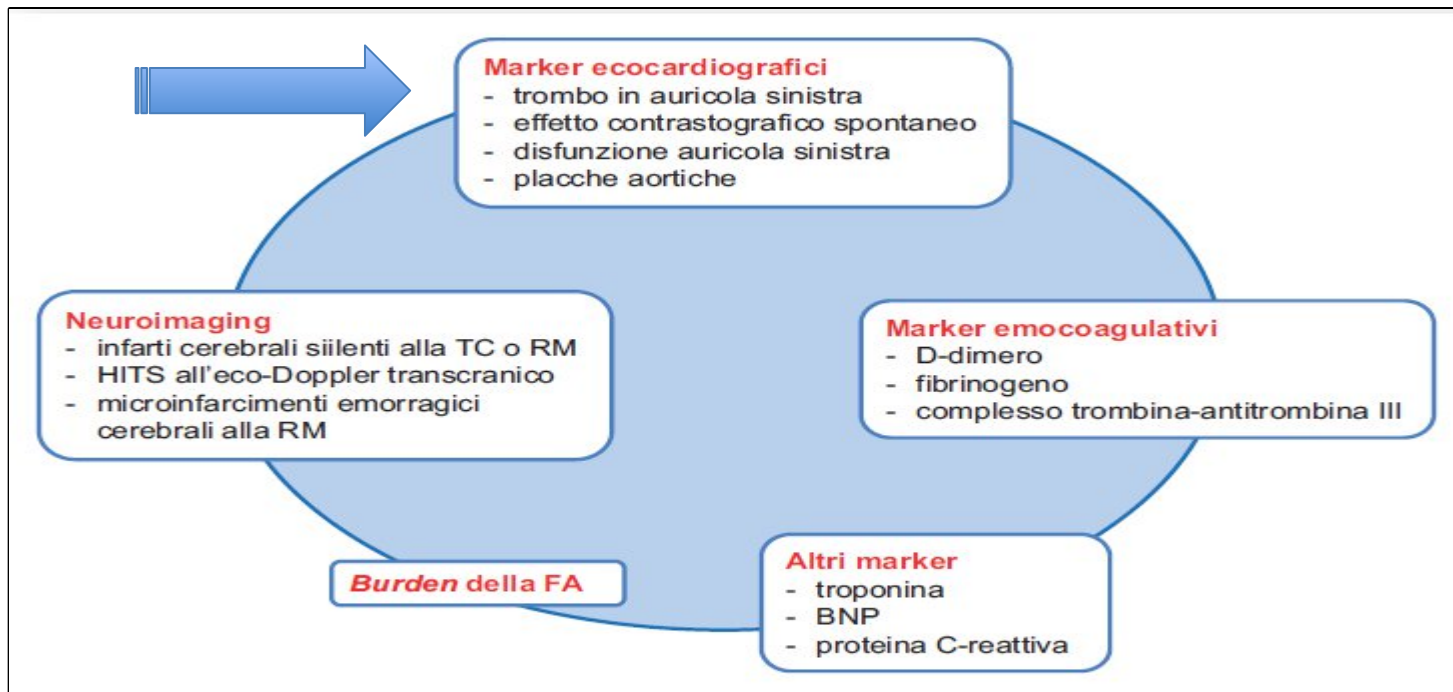
Nedios S, Heart Rhythm, dec 2014
Leipzig Heart Center AF Ablation Registry





- ..regardless CHA₂DS₂Vasc..
- How is the risk?

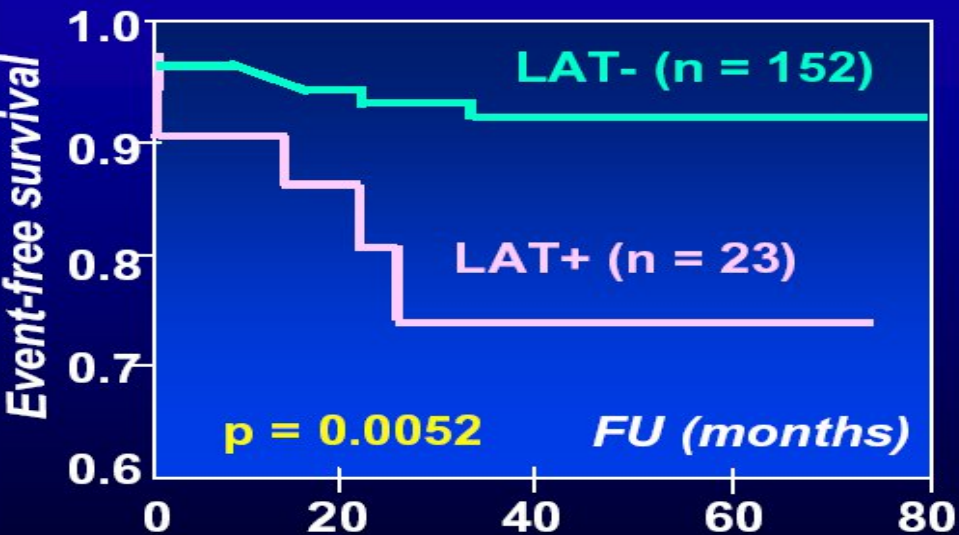
Marker Ecocardiografici di Rischio di Stroke nella FANV



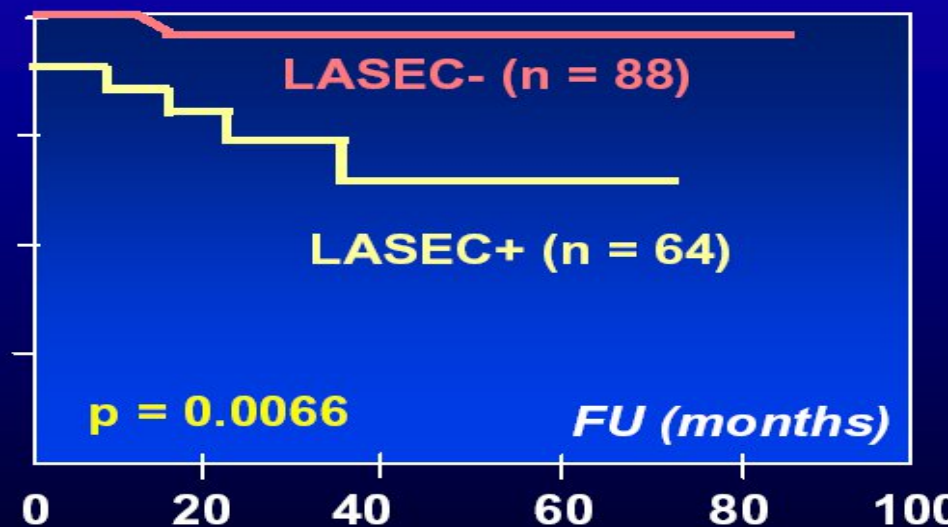
Cardiovascular death in AF pts with or without TEE abnormalities

Down et al, JASE 2005

Left atrial / appendage
thrombus (LAT)

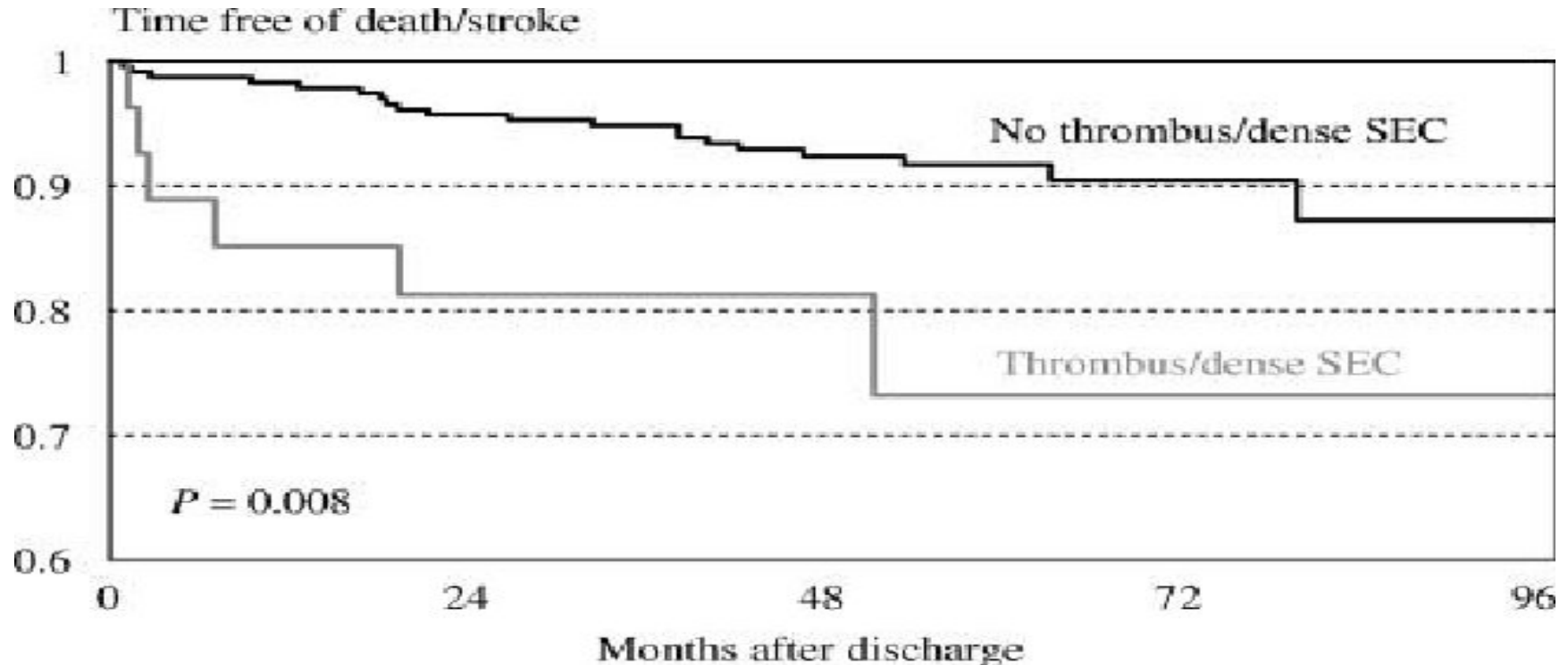


Left atrial spontaneous
EchoContrast (LASEC)

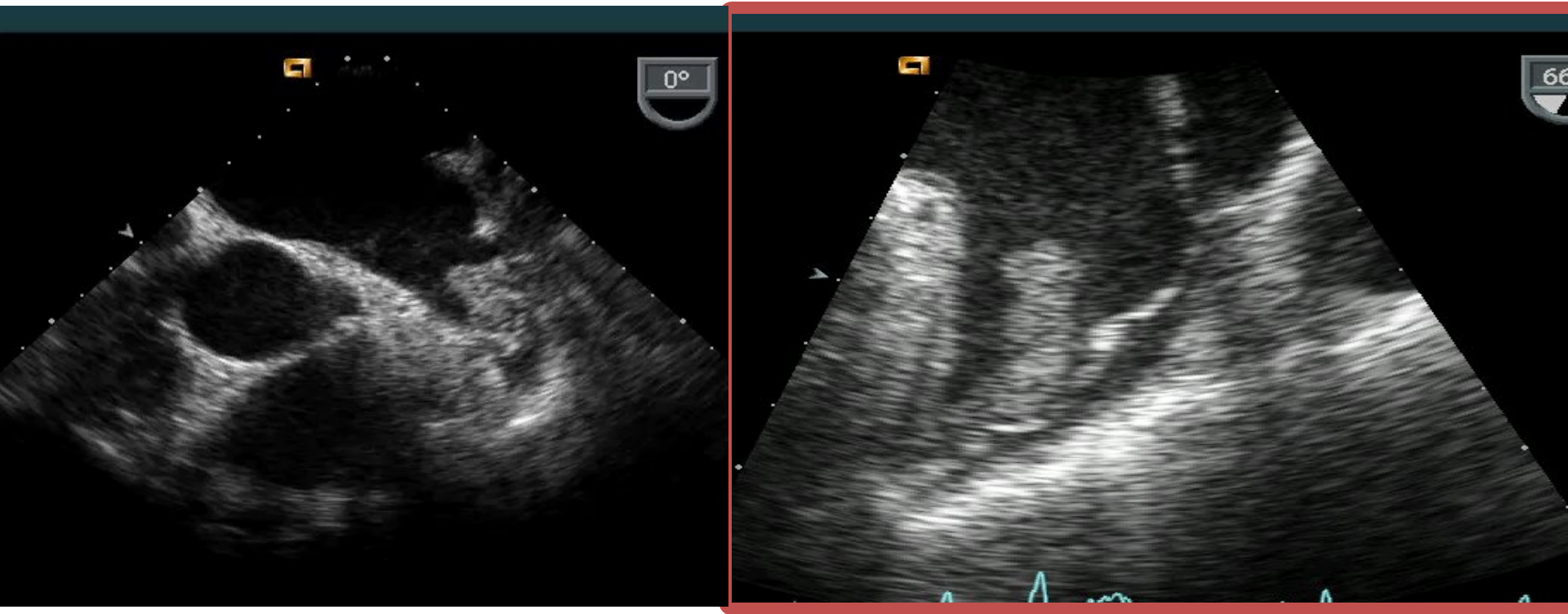


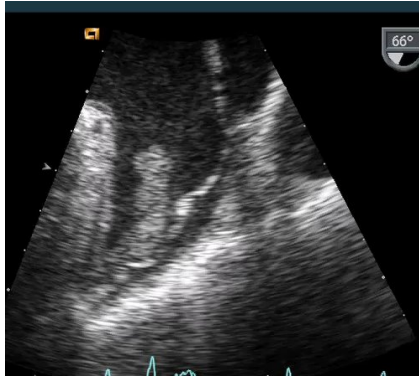
Prevalence and clinical impact of LA thrombi/dense echocontrast in AF and low (0-1) CHADS₂ score

Kleeman et al, EJE 2008



How to resolve them?





Over the years..

Warfarin!!!!

Fate of Left Atrial Thrombi in Patients With Atrial Fibrillation Determined by Transesophageal Echocardiography and Cerebral Magnetic Resonance Imaging

Peter Bernhardt, MD, Harald Schmidt, MD, Christoph Hammerstingl, MD,
Matthias Hackenbroch, MD, Torsten Sommer, MD, Berndt Lüderitz, MD, PhD, and
Heyder Omran, MD

Am J Cardiol, 2004

43 pts with
permanent NVAF +
LAA thrombus

Effective **VKA** therapy
(INR=2-3) ☾ 12 months
F-U



Thrombus Resolution= 56%

**No Thrombus
Resolution= 44%**

Cere
16%

Predictors=

- LAA low peak emptying velocities,
- History of thromboembolism

Bernhardt P, Am J Cardiol 200

Message

- LA thrombi persist in up to 40% of patients under VKA treatment and it is associated with poor prognosis..

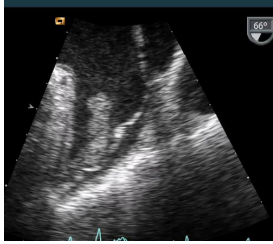
Bernhardt P, Am J Cardiol 2004

Blood Stasis Secondary to Heart Failure Forms Warfarin-Resistant Left Atrial Thrombus

Atai WATANABE,¹ MD, Naohide YAMASHITA,¹ MD, *and* Takeshi YAMASHITA,² MD

Int Heart J, 2014;55

431 pts with NVAF and without LA thrombus received warfarin (at a dose and duration sufficient for increasing INR to ≥ 2 for ≥ 30 days)
10 pts (2,3%) **LA thrombus formation**

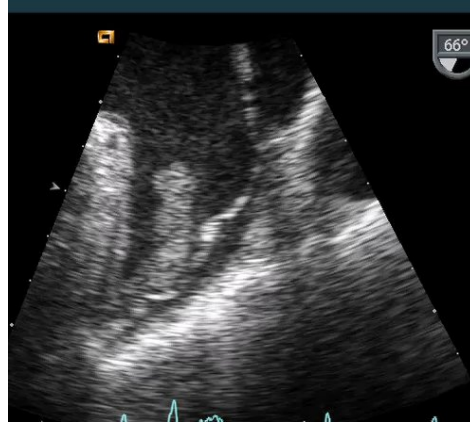


Predictors of thrombus formation:

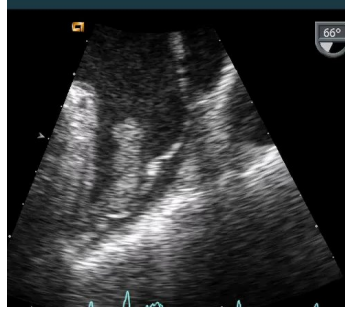
- RVsP
- Low LAA flow velocity
- LA dimensions
- High LV mass
- **Low LVEF**

**Blood Stasis=
warfarin resistance!!**

Watanabe A, Int Heart J, 2014



Why not NOACs?



NOAC

No indications from:

- RELY
- ROCKET
- ARISTOTLE

Dabigatran Versus Warfarin in Patients With Atrial Fibrillation

An Analysis of Patients Undergoing Cardioversion

Rangadham Nagarakanti, MD; Michael D. Ezekowitz, MBChB, DPhil, FRCP, FACC;
Jonas Oldgren, MD, PhD; Sean Yang, MSc; Michael Chernick, PhD; Timothy H. Aikens, BA;
Greg Flaker, MD; Josep Brugada, MD; Gabriel Kamenský, MD, PhD, FESC; Amit Parekh, MD;
Paul A. Reilly, PhD; Salim Yusuf, FRCPC, DPhil; Stuart J. Connolly, MD

	D 110	D 150	Warfarin
TEE Thrombi	1.8%	1.2%	1.1%

1270 pts

p=n.s.



Left atrial thrombus resolution in atrial fibrillation or flutter: Results of a prospective study with rivaroxaban (X-TRA) and a retrospective observational registry providing baseline data (CLOT-AF)

Gregory Y. H. Lip, MD,^{a,b} Christoph Hammerstingl, MD,^c Francisco Marin, MD,^d Riccardo Cappato, MD,^e Isabelle Ling Meng, MD,^f Bodo Kirsch, MSc,^g Martin van Eickels, MD,^f and Ariel Cohen, MD^h, on behalf of the X-TRA study and CLOT-AF registry investigators¹ *Birmingham, United Kingdom; Aalborg, Denmark; Bonn, Germany; Murcia, Spain; Rozzano, Italy; Berlin, Germany; and Paris, France*

Am Heart J 2016;178:126-34.)

X-TRA

(prospective study)

Screened and enrolled
N = 61 patients

Screening failures
n = 1 patient

Rivaroxaban

Eligible for inclusion
(ITT)
n = 60 patients

Observation incomplete
n = 4 patients

Primary reason:

- Adverse event (n = 2)*
- Death (n = 1)†
- Logistic difficulties (n = 1)

Observation of 6-8 weeks
completed
n = 56 patients

No baseline thrombus
n = 3 patients

Baseline and EOT TEE available
(mITT)
n = 53 patients

CLOT-AF

(retrospective registry)

Screened and enrolled
N = 159 patients

All anticoagulants

Screening failures
n = 3 patients

Eligible for inclusion
(ITT)
n = 156 patients

Observation period incomplete
n = 45 patients

Primary reason:

- "Lost to follow-up"‡ (n = 38)
- Death (n = 1)§
- Other (n = 6)

Observation period
of 3-12 weeks completed
n = 111 patients

Baseline and EOT TEE available
(mITT)
n = 96 patients

Lip G,
Am Heart J
2016;178:126-34

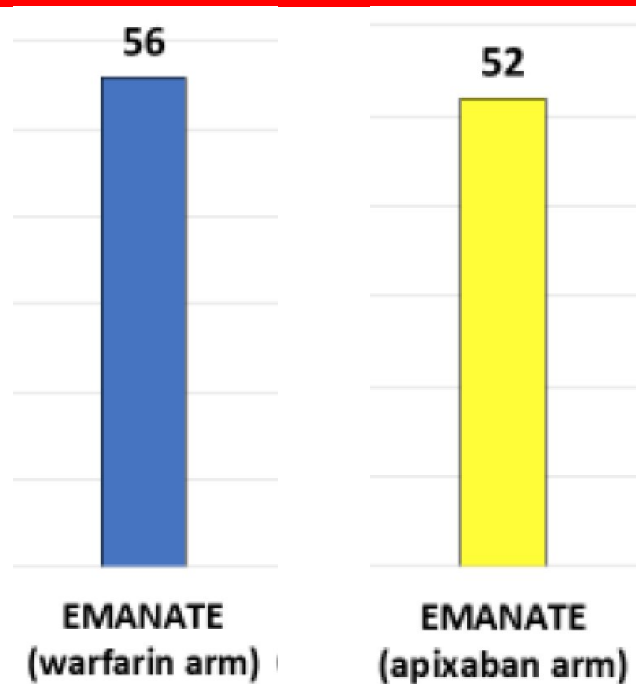


Thrombus resolution

	Evaluation set	Total n	n thrombus resolved	%	95% CI
Prospective X-TRA study					
Complete thrombus resolution (assessed by blinded adjudicators)*	mITT	53	22	41.5	28.1-55.9
Complete thrombus resolution (assessed by blinded adjudicators), worst-case scenario considering subjects without EOT TEE as nonresolved	ITT	60	22	36.7	24.6-50.1
Resolved or reduced thrombus (assessed by blinded adjudicators) [†]	mITT	53	32	60.4	46.0-73.6
Retrospective CLOT-AF registry					
Complete thrombus resolution	mITT	96	60	62.5	52.0-72.2
Complete thrombus resolution by region					
Eastern Europe	mITT	46	26	56.5	41.1-71.1
Western Europe	mITT	50	34	68.0	53.3-80.5
Complete thrombus resolution, worst-case scenario considering subjects without EOT TEE as nonresolved	ITT	156	60	38.5	30.8-46.6
Complete thrombus resolution, best-case scenario considering subjects without EOT TEE as resolved	ITT	156	120	76.9	69.5-83.3

Apixaban (EMANATE)

LAA-Thrombus Resolution (%)



Ezekowitz M, Eur H J 2018

doi: 10.1016/j.jstrokecerebrovasdis.2014.11.031. Epub 2015 Jan 22.

Embolic stroke during apixaban therapy for left atrial appendage thrombus

Masaki Ohyagi¹, Kazuha Nakamura², Mutsufusa Watanabe², Hiroto Fujigasaki²

- Here we report a patient who experienced embolic stroke while taking apixaban for the treatment of LAA thrombus.
- Thrombolysis therapy was initiated at the onset of stroke and the patient recovered remarkably.
- **Apixaban is known to make thrombi mobile and/or fragile by shifting the coagulation/fibrinolysis balance** to a relative predominance of fibrinolytic activity; therefore, it is necessary to monitor for thromboembolic complications after the initiation of apixaban for the treatment of pre-existing LAA thrombus.



Journal of
Clinical Medicine

2022



Article

A Prospective Study to Evaluate the Effectiveness of Edoxaban for the Resolution of Left Atrial Thrombosis in Patients with Atrial Fibrillation

Giuseppe Patti ^{1,†} , Vito Maurizio Parato ^{2,†} , Ilaria Cavallari ³, Paolo Calabrò ^{4,5} , Vincenzo Russo ⁶ ,
Giulia Renda ⁷, Felice Gragnano ^{4,5} , Vittorio Pengo ⁸ , Antonio D'Onofrio ⁹, Massimo Grimaldi ¹⁰
and Raffaele De Caterina ^{11,12,13,*} 



This is a non-controlled, observational, prospective, open-label pilot study, performed in seven Italian centers:

- “SS. Annunziata” Hospital, G. d’Annunzio University of Chieti (coordinating center);
- Campus Bio-Medico University Hospital of Rome;
- Cardiology Clinic, University of Padua;
- “Madonna del Soccorso” Hospital, S. Benedetto del Tronto;
- “Sant’Anna e San Sebastiano” Hospital, Caserta;
- Monaldi Hospital of Naples;
- F. Miulli Regional General Hospital, Acquaviva delle Fonti.

Patients with non-valvular AF and LA or LAA thrombosis documented at transesophageal echocardiography (TEE) were included

EDO-study

Single arm, multicentre, prospective, open-label, pilot, interventional study..

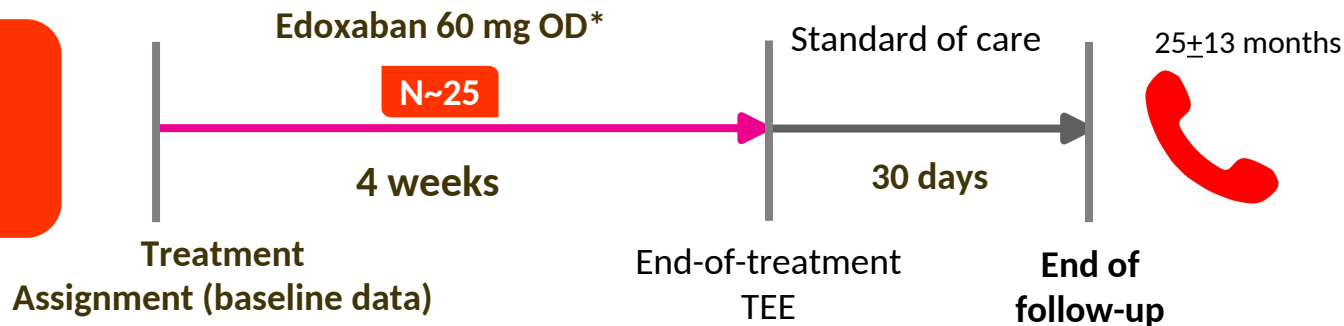
Objective: efficacy of edoxaban OD for the treatment of a **left atrial (LA)/left atrial appendage (LAA) thrombus** in subjects with NVAF or atrial flutter.

Primary and Secondary Endpoints*

•Efficacy:

- percentage of patients with complete resolution of LA or LAA thrombus at the end of treatment after 4 weeks
- complete resolution is specified as the subjects is completely thrombus free confirmed on TEE

Study Population:
NVAF or atrial flutter
with LA/LAA thrombus
detected via TEE



*CrCl 15-49 ml/min, body weight ≤60 Kg, P-G inhibitors intake: 30 mg OD

EDO-study

Table 1. Main demographic/clinical features of the study population.

	<i>n</i> = 25
Age (years)	68.3 ± 10.8
Female gender	4 (16)
BMI (kg/m ²)	28.1 ± 7.8
AF duration (years)	4.3 ± 1.7
Previous stroke	3 (12)
Heart failure	11 (44)
Arterial hypertension *	24 (96)
Diabetes mellitus **	4 (16)
COPD	6 (24)
Vascular disease	11 (44)
CHA ₂ DS ₂ -VASc score	3.2 ± 1.5
HAS-BLED score	1.9 ± 1.1
Baseline data	
Systolic blood pressure	127.7 ± 45.7
Diastolic blood pressure	76.4 ± 26.9
Heart rate (beats/min)	84.2 ± 30.3
Creatinine clearance (Cockroft–Gault, mL/min)	76.4 ± 20.3
Hemoglobin (g/dL)	13.5 ± 3.2
Platelet count (<i>n</i> /μL)	222,296 ± 67,310

EDO-study

Edoxaban dose	
60 mg	23 (92)
30 mg	2 (8)

Concomitant therapies	
Beta-blockers	19 (76)
Calcium channel blockers	9 (36)
Amiodarone	1 (4)
Digoxin	2 (8)
Propafenone	1 (4)
Hydroquinidine	1 (4)
Antiplatelet agents	6 (24)
ACE inhibitors/ angiotensin receptor blockers	17 (68)
Diuretic agents	13 (52)

Table 2. Echocardiographic parameters at baseline.

	<i>n</i> = 25
TTE findings at baseline	
Maximum indexed left atrial diameter (mm/m ²)	30.6 ± 12.5
Left ventricular ejection fraction (%)	43.6 ± 20.9
Indexed left atrial volume (mL/m ²)	44.4 ± 13.4
Indexed left ventricular end-diastolic volume (mL/m ²)	67.7 ± 38.8
Left ventricular hypertrophy	13 (52)
Mitral regurgitation (moderate to severe)	6 (24)
Aortic valve disease (moderate to severe)	4 (16)
PASP (mmHg)	35.2 ± 12.7
TAPSE (mm)	18.3 ± 4.0
TEE findings at baseline	
Spontaneous left atrial echo contrast (at least moderate)	10 (40)
Left atrial velocity (cm/s)	23.5 ± 10.9
Site of thrombosis	
LAA	25 (100)
Other	-
Multilobes LAA	6 (24)
Thrombus characteristics	
Ovoid	14 (56)
Pedunculated	11 (44)
Thrombus measures	
Maximum thrombus area (mm ²)	70.2 ± 59.8

*END-POINTS

The **primary efficacy outcome** was:

the percentage of patients after 4 weeks of edoxaban treatment with **complete thrombus resolution** by TEE imaging, using the following probe angulations: 0°, 45° to 60°, and 90°;

Secondary endpoints were:

- The percent variation of thrombus area at 4 weeks by TEE (probe angulations: 0° , 45° , to 60° , and 90°);
- The incidence of thromboembolic events at 4 and 8 weeks (stroke/TIA/systemic embolism, assessed by a telephone interview).



Results

- There was a **complete thrombus resolution** in **14/25** patients (**56%**) at 4 weeks.
- In patients with residual atrial thrombosis (n = 11), we observed a **15.4±14.9% reduction** in the thrombus area from baseline.
- As compared with patients without thrombus dissolution, those with **thrombus resolution** had:
 1. *a numerically lower-indexed LA diameter* (27.9 ± 9.3 vs 34.8 ± 16.1 mm/m²),
 2. *a smaller maximum thrombus area* at baseline (45.5 ± 44.6 vs 63.9 ± 43.5 mm²),
 3. *a higher left ventricular ejection fraction* ($47.4 \pm 21.0\%$ vs $38.4 \pm 20.6\%$),
 4. *higher maximum LAA flow velocities* (26.3 ± 15.2 vs 19.3 ± 10.0 cm/s).
 5. *Shorter AF duration..*

Table 3. Baseline characteristics in patients with and without thrombus resolution after 4 weeks of edoxaban therapy.

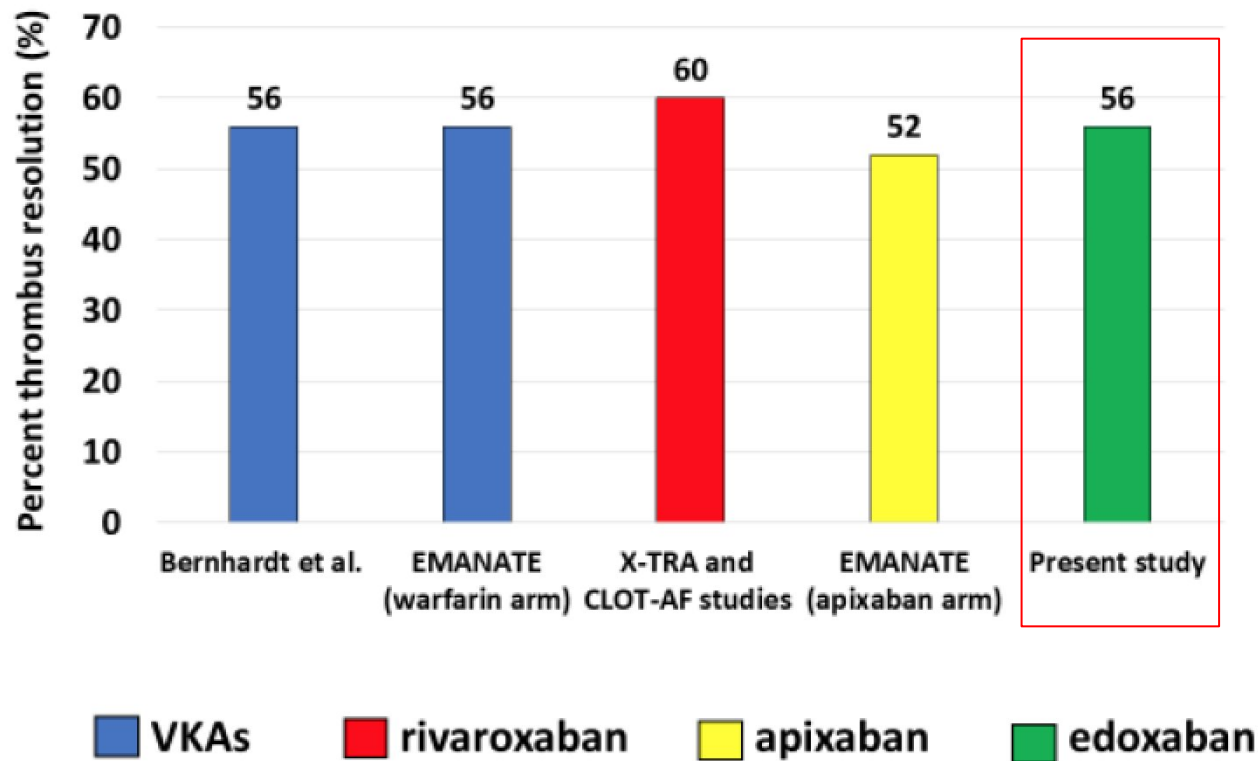
	Thrombus Resolution (<i>n</i> = 14)	No Thrombus Resolution (<i>n</i> = 11)
Age (years)	68.4 ± 10.6	67.7 ± 11.6
Female gender	3 (21)	1 (9)
BMI (kg/m ²)	28.0 ± 9.6	28.3 ± 4.9
AF duration (years)	3.5 ± 1.4	4.5 ± 1.8
Arterial hypertension	14 (100)	10 (91)
Diabetes mellitus	2 (14)	2 (18)
Heart failure	5 (36)	6 (55)
CHA ₂ DS ₂ -VASc score	3.2 ± 1.3	3.4 ± 1.2
Left ventricular ejection fraction (%)	47.4 ± 21.0	38.4 ± 20.6
Maximum indexed left atrial diameter (mm/m ²)	27.9 ± 9.3	34.8 ± 16.1
Indexed left ventricular end-diastolic volume (mL/m ²)	62.8 ± 34.1	76.0 ± 48.5
At least moderate mitral/aortic valve disease	4 (28)	3 (27)
No. of LAA lobes	1.4 ± 0.7	1.6 ± 1.0
Spontaneous echo contrast grade	1.8 ± 0.8	2.0 ± 1.1
LAA flow velocity (cm/s)	26.3 ± 15.2	19.3 ± 10.0
Ovoid thrombus at enrollment	7 (50)	7 (64)
Maximum thrombus area at enrollment (mm ²)	45.5 ± 44.6	63.9 ± 43.5
Edoxaban dose		
60 mg	13 (93)	10 (91)
30 mg	1 (7)	1 (9)



25_±13 months

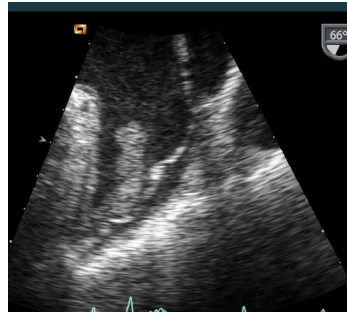
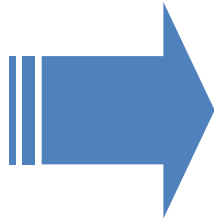


- No stroke/TIA/systemic embolism occurred..
- Three patients died (one from a myocardial infarction)..
- Two patients had a major bleeding (on edoxaban treatment).
- Of the 11 patients with residual atrial thrombus at 4 weeks, three patients were switched to warfarin ☾ TEE, repeated after a mean of 2 months, revealed thrombus resolution.
- Eight patients continued edoxaban treatment ☾ TEE was repeated in four patients after a mean of 3 months, demonstrating thrombus resolution,
- ... the remaining four patients did not undergo further TEE examination and experienced no clinical events.



Conclusions

**Xa inhibitors may be a valuable option
for dissolving LAA thrombus..**





Thanks!

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