

# **Atrial Fibrillation**

## **Risk Marker vs. Risk Factor**

## **Marker vs. Mechanism**

## **AF Stasis, clot formation, embolism**

**Heart House,  
26<sup>th</sup> March, 2015**

**John Camm**



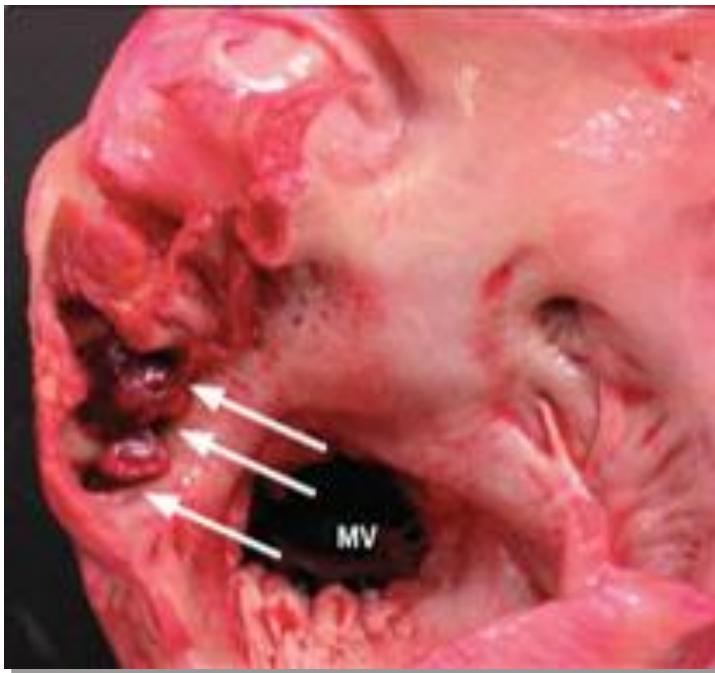
# Virchow's Triad

- 1) Abnormal changes in flow are evident by stasis in the left atrium, and seen as spontaneous echocontrast**
- 2) Abnormal changes in vessel walls—essentially, anatomical and structural defects—include progressive atrial dilatation, endocardial denudation, and oedematous or fibroelastic infiltration of the extracellular matrix.**
- 3) Abnormal changes in blood constituents are well described, and include haemostatic and platelet activation, as well as inflammation and growth factor changes.**

After Wilson and Lip: *Lancet* 2009; 373: 155–66

# LAA and Thrombus

- Thrombus present in 12.6% of patients (47% in valvular HD - mostly rheumatic MS).
- 90% of the thrombi were found in the LAA in non-rheumatic AF

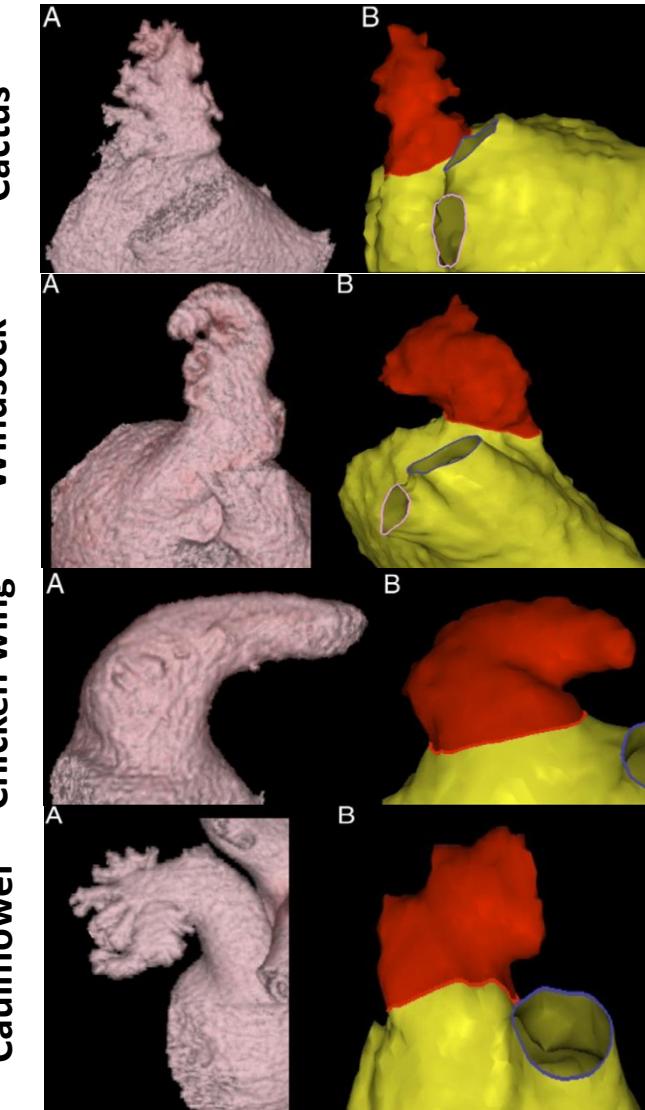
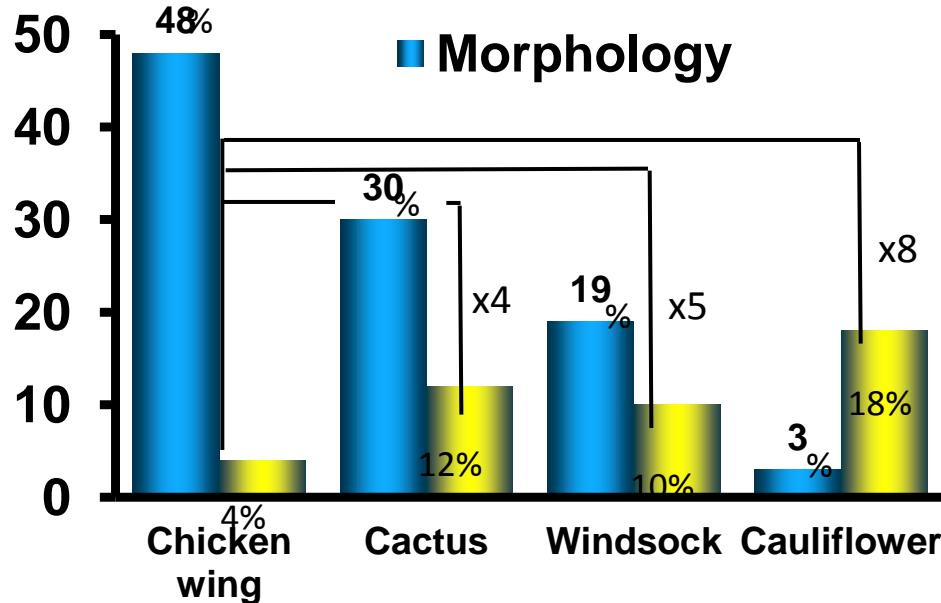


Setting	N	LAA	LA body	Reference
TEE	317	66	1	Stoddard; JACC '95
TEE	233	34	1	Manning; Circ '94
Autopsy	506	35	12	Aberg; Acta Med Scan '69
TEE	52	2	2	Tsai; JFMA, '90
TEE	48	12	1	Klein; Int J Card '93
TEE & Op <sup>n</sup>	171	8	3	Manning; Circ '94
SPAF III TEE	359	19	1	Klein; Circ '94
TEE	272	19	0	Leung; JACC '94
TEE	60	6	0	Hart; Stroke '94
Total	2018	201	21	

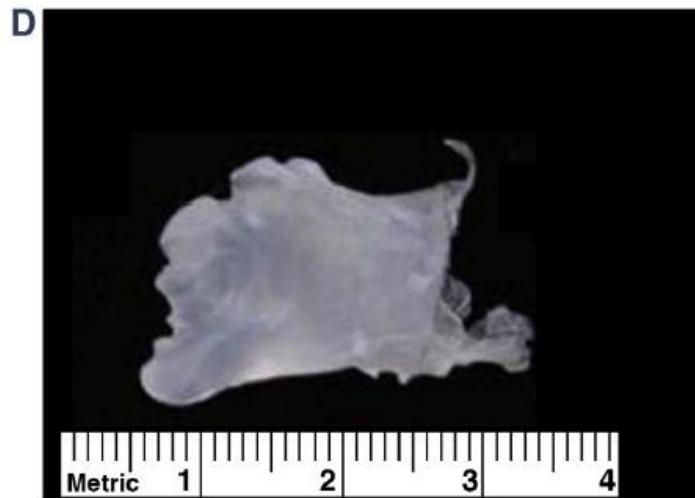
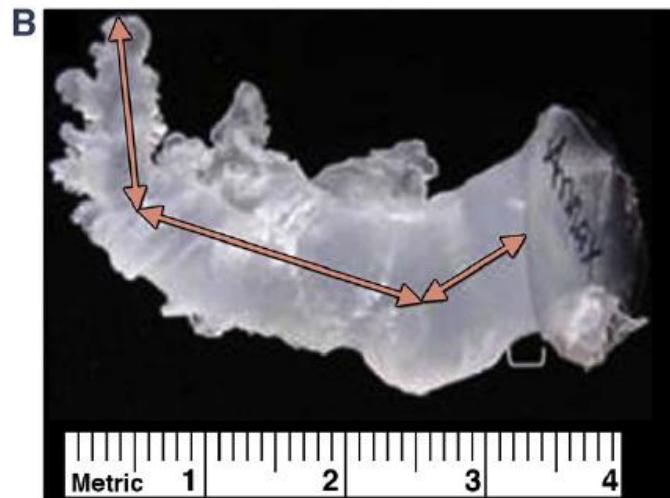
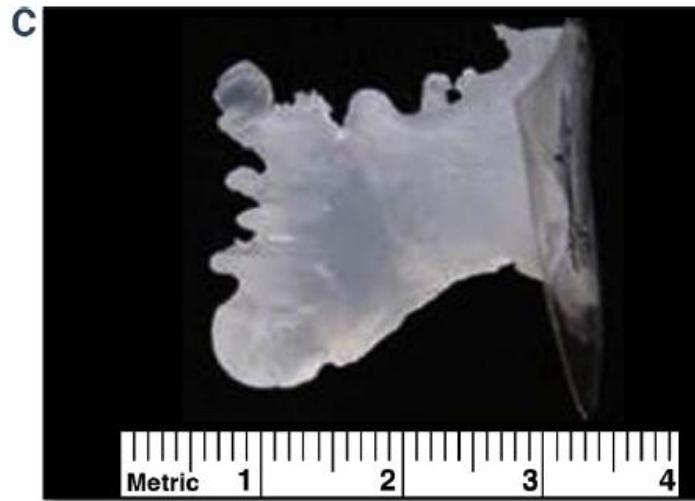
Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996;61:755–9.

# LAA Morphology and Risk of Stroke

- N = 932 for AF ablation, (59±10 yrs, 79% men)
- PAF: 59%, persistent AF: 36%
- CHADS<sub>2</sub> 1: 40%, CHADS<sub>2</sub> ≥ 2: 14%
- CT: n = 499, MRI: n = 433
- Stroke/TIA; n = 78 (8%)



# Left Atrial Appendage Morphology



## LAA Casts

(A) Chicken wing. (B) Windsock. (C) Cauliflower. (D) Cactus. A, B and C, D are pairs of the same casts but viewed from different perspectives showing the overlap that exists regarding LAA morphology.

# PROTECT-AF: Final Results

463 patients received the Watchman and 244 warfarin management

Average CHADS<sub>2</sub> scores 2.2 and 2.3, respectively

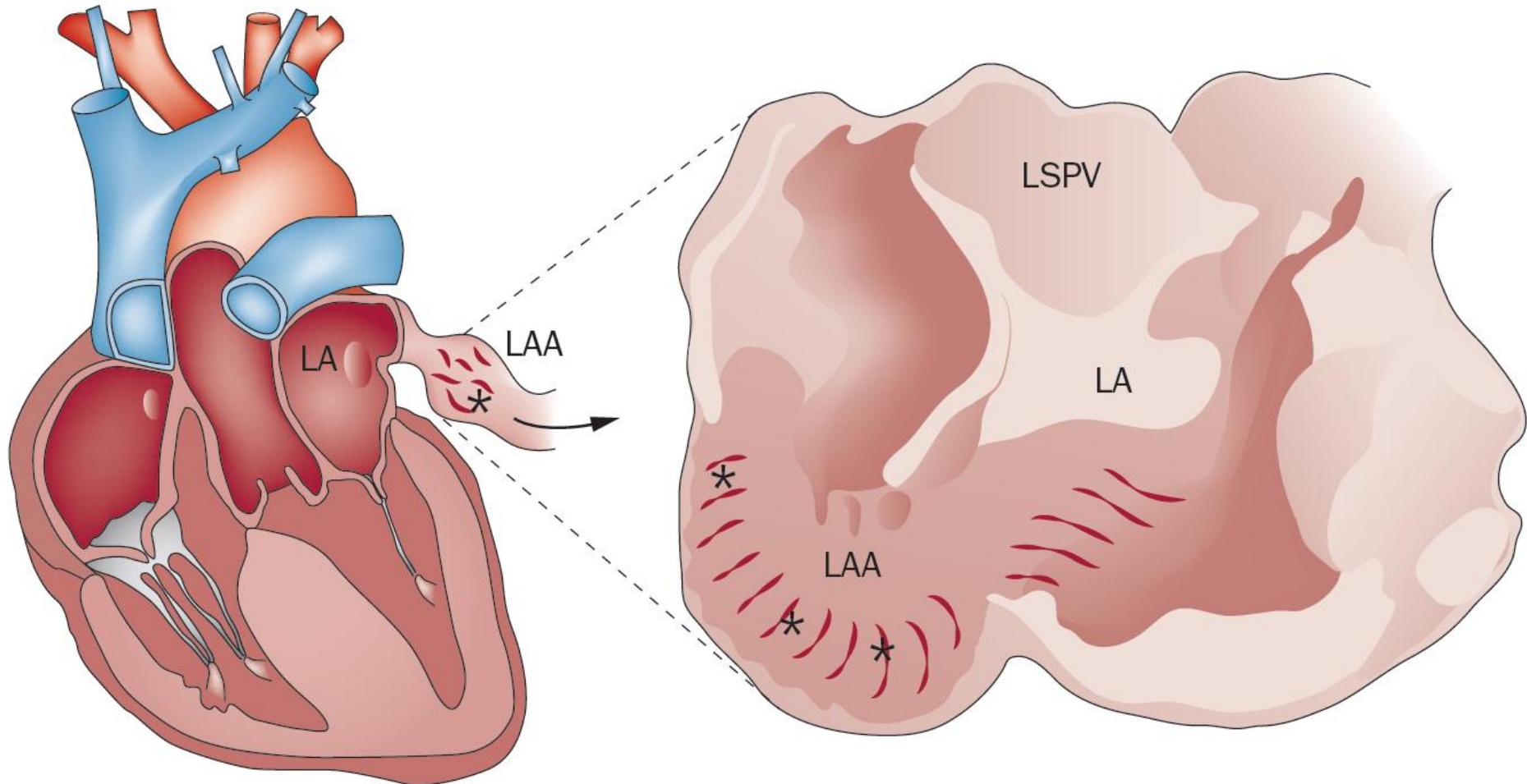
Mean follow-up: 45 months

Rate Ratios (95% CI) for Primary Efficacy and Safety End Points and Secondary End Points in PROTECT-AF, by Intention to Treat

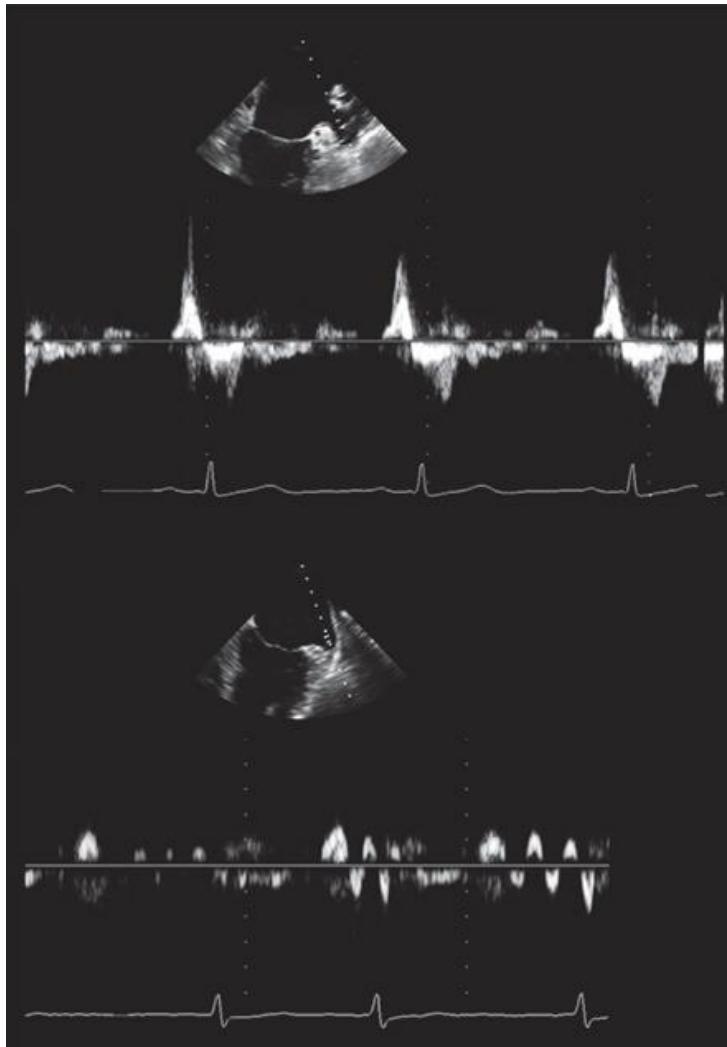
End points (2621 pt/years)	RR (95% CI)
Primary efficacy end point: Stroke, systemic embolism, or cardiovascular or unexplained death	0.60 (0.41–1.05)
All-cause mortality	0.66 (0.45–0.98)
Cardiovascular mortality	0.40 (0.21–0.72)
Hemorrhagic stroke	0.15 (0.03–0.49)
Primary safety end point: serious pericardial effusion, major bleeding, procedure-related stroke, hemorrhagic stroke, and device embolization	1.17 (0.78–1.95)

Reddy VY, et al. 2013

# The Left Atrial Appendage



# Left Atrial Appendage Flow Velocity



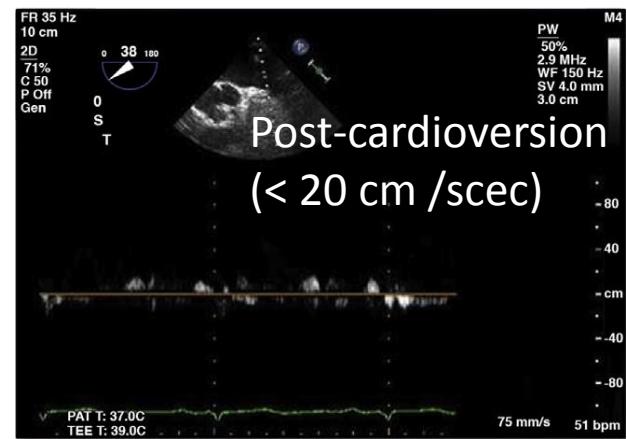
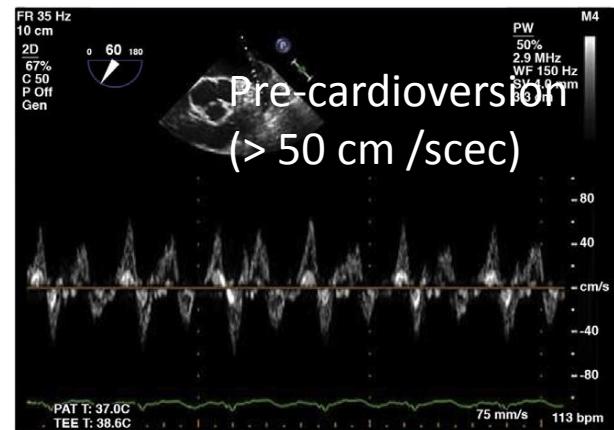
- SR: 4 waves - forward flow ( $0.46 \pm 0.18$  cm/s), probably owing to LAA contraction and emptying; retrograde wave that represents LAA filling ( $0.46 \pm 0.17$  cm/s). Then, additional forward and retrograde waves ( $0.23 \pm 0.10$  cm/s and  $0.22 \pm 0.11$  cm/s resulting from ventricular relaxation and LAA elasticity
- Heavily dependent on loading conditions and left ventricular function
- LAA outflow velocity - parameter most-significantly correlated with SEC.
- Velocities  $<40$  cm/s are associated with higher risk of stroke and the presence of SEC with decreasing velocities of  $<20$  cm/s associated with the identification of thrombus within the LAA

# Atrial Stunning

LAA flow velocities tend to diminish and SEC can develop immediately after pharmacological or electrical cardioversion, probably due to atrial stunning

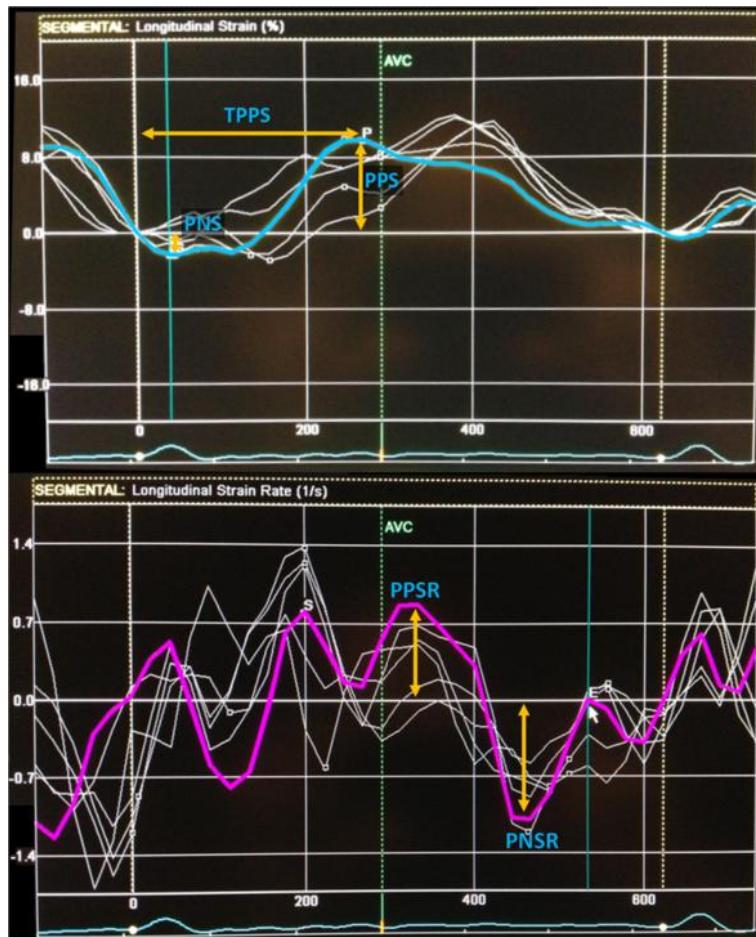
Could indicate a myopathic process, because the duration of AF is related to the degree of impaired left atrial or LAA function (does not occur after DCCV for VT/VF)

Full recovery of atrial stunning is achieved within 24 h in patients with brief AF (<2 weeks), within 1 week in patients with AF of moderate duration (2–6 weeks), and within 1 month in patients with prolonged AF (>6 weeks)



# Speckle Tracking , Strain Rates

## Atrial Thrombus



82 assessed patients  
LAA thrombi/sludge in 16 (19.5%)

+ve correlation between peak positive strain rate and maximum emptying velocity ( $r = 0.589$ ;  $P <0.001$ ) and maximum filling velocity of the LAA ( $r = 0.651$ ;  $P <0.001$ )

Peak negative strain rate associated with maximum emptying velocity ( $r = -0.513$ ;  $P <0.001$ ) and maximum filling velocity of the LAA ( $r = -0.552$ ;  $P <0.001$ )

AF duration, PNSR and time-to-peak positive strain independent predictors of LAA thrombi or sludge on multivariate analysis logistic regression

# Spontaneous Echo Contrast (SEC)

- SEC is present in approximately 50% of patients with AF
- ~2% of patients in normal sinus rhythm
- Approximately 40% of patients with nonvalvular AF will develop SEC 2 years after the onset of the arrhythmia
- SEC will persist indefinitely unless AF is terminated
- Mitral regurgitation increases the flow velocity in the left atrium and, therefore, protects patients with AF from developing SEC and thrombi
- SEC is present in 90% of patients with LAA thrombus, and is the cardiac factor most-strongly associated with LAA thrombus formation, stroke and other embolic events, and reduced survival
- Two parameters, left atrial dilatation and low LAA emptying and filling velocities, have been shown to be predisposing factors for SEC and thrombus formation

# Variables Predicting LAA Thrombus

## Transesophageal echocardiography (TEE)

564 patients, of whom LAA thrombus was observed in 36 (6.4%) pts

### Multivariate analysis:

CHADS<sub>2</sub>(Congestive heart failure, Hypertension, Age>75, Diabetes mellitus and prior Stroke or transient ischemic attack) score ( $P=0.002$ )

Left ventricular ejection fraction ( $P=0.01$ )

degree of spontaneous echo contrast ( $P=0.02$ )

Left atrial volume ( $P=0.02$ ),

Number of LAA lobes ( $P<0.001$ ) (Usually more than 3)

independently associated with thrombus formation.

LAA volume significantly decreased in patients maintaining sinus rhythm after catheter ablation ( $P=0.0009$ ).

**Complex LAA morphology characterized by an increased number of LAA lobes was associated with the presence of LAA thrombus independently of clinical risk**

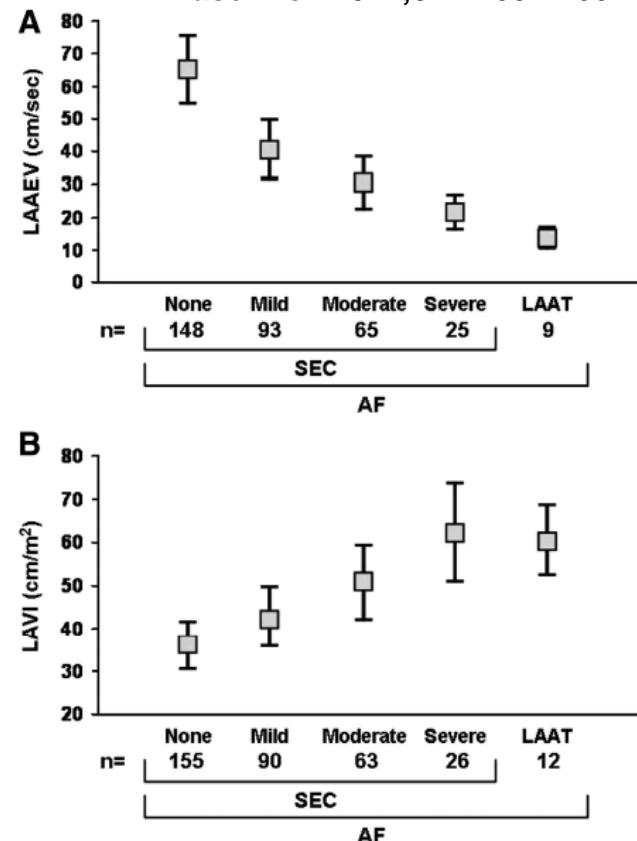
# Association between VWF and SEC Thrombotic Propensity in AF

## Left atrial appendage size and function and whole blood stasis

Association between measures of whole blood stasis (spontaneous echo contrast [SEC]) and left atrial appendage thrombus (LAAT) and either left atrial appendage emptying velocity (LAAEV) (A) or left atrial volume index (LAVI)

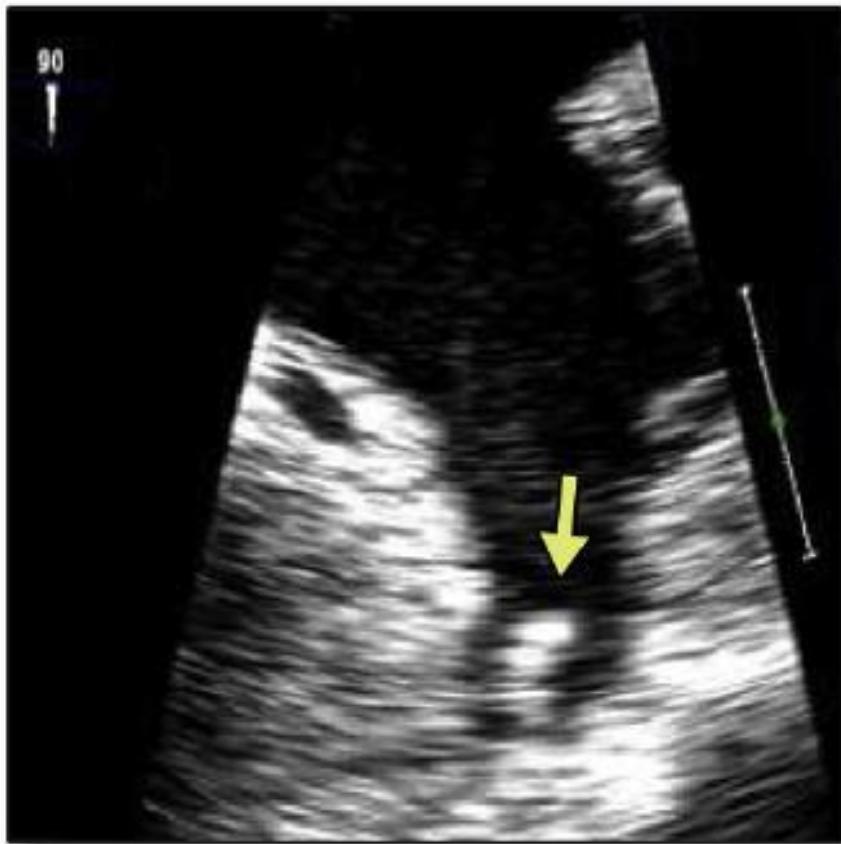
AF patients with LAAT had higher VWF: Ag (20061 versus 15552,  $P=0.0006$ ) and VWF: Act (17957 versus 14151  $P=0.0026$ ) compared with those without LAAT.

Naser A, et al. Arterioscler Thromb Vasc Biol. 2011;31:2760-2766



414 consecutive pts with non-valvular AF (age  $63\pm13$  years; 25% women) and in 100 pts (age  $64\pm14$  years; 39% women) with NSR

# Improved Diagnosis of LAA Pectinate



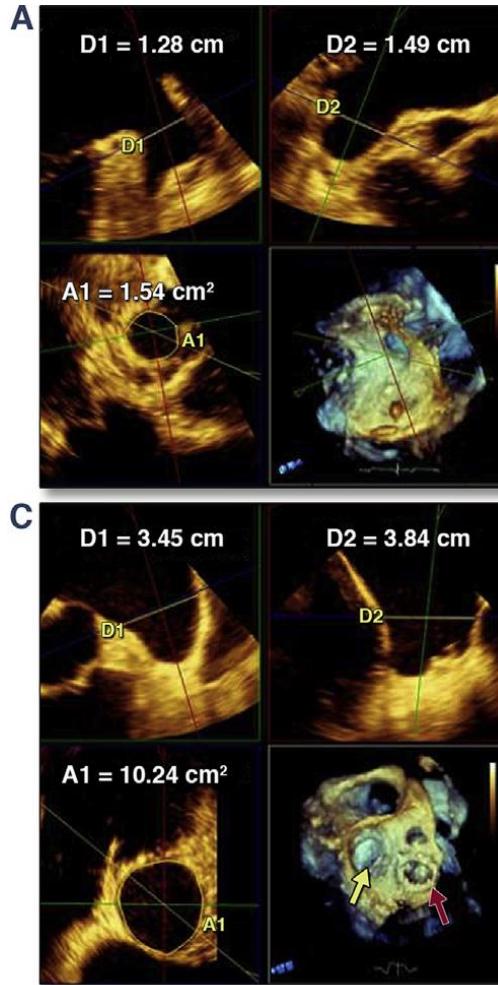
Possible Clot



Obvious Pectinate

# Diameter and Area Changes of the LAA Orifice During the Cardiac Cycle

Sinus Rhythm



Atrial Fibrillation

Difference in area between systole and diastole in the patients in SR

Minimal change in the area in the patient in AF where there is considerably reduced contractility.

LAA orifice is markedly enlarged

AF is associated with structural remodeling of the LAA

which includes dilation of the chamber and reduction in pectinate muscles (not shown)

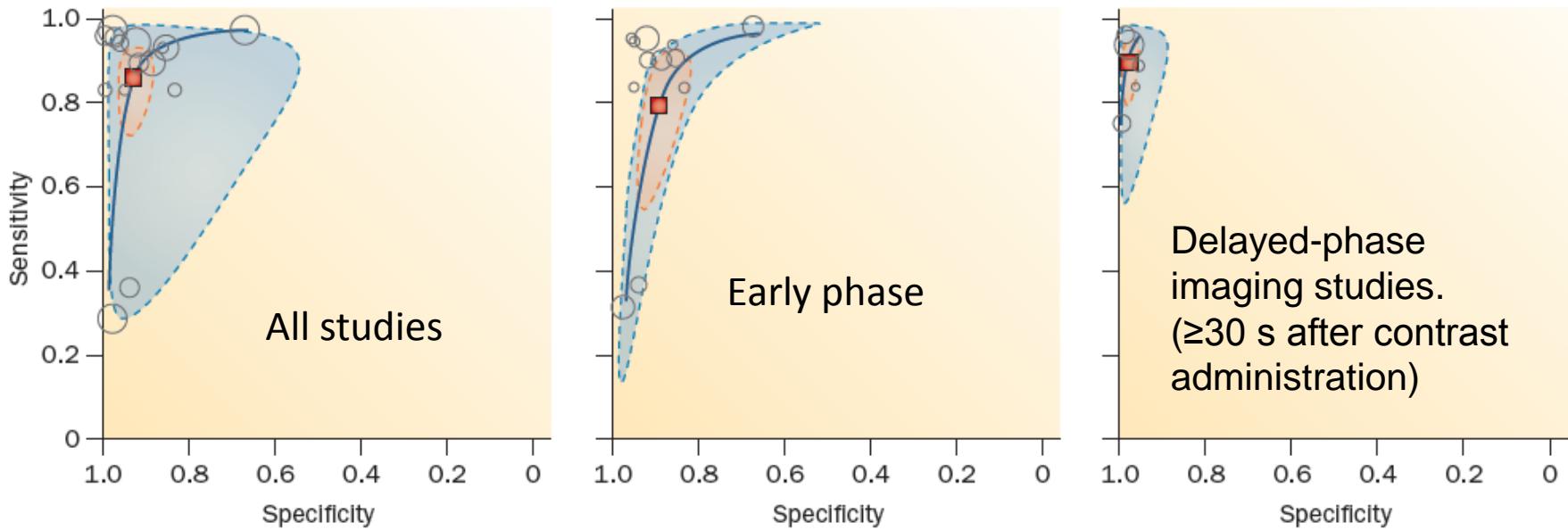
# Comparison of the Different Imaging Modalities for Assessment of the LAA

	TEE	MDCT	CMR
Sensitivity/specificity for LAA thrombi detection	92%-100%/ 98%-99%	96%/92%	67%/44%
Spatial resolution	0.2-0.5 mm	0.4 mm	1-2 mm
Temporal resolution	20-33 ms	70-105 ms	30-50 ms
3D volume rendering	Yes (with 3D)	Yes	Yes
Contrast required	No*	Yes	No*
Ionizing radiation	No	Yes	No
Special considerations	Widely available, provides real-time assessment  Semi-invasive	Noninvasive, dynamic assessment of LA function  Cannot be performed real-time during procedures  Limited availability	Noninvasive, cannot be performed real-time during procedures  Limited availability Cannot be performed in patients with pacemakers

Beigel R, et al. J Am Coll Cardiol Img 2014;7:1251–65

# Detection of LAA Thrombus in AF by Cardiac CT

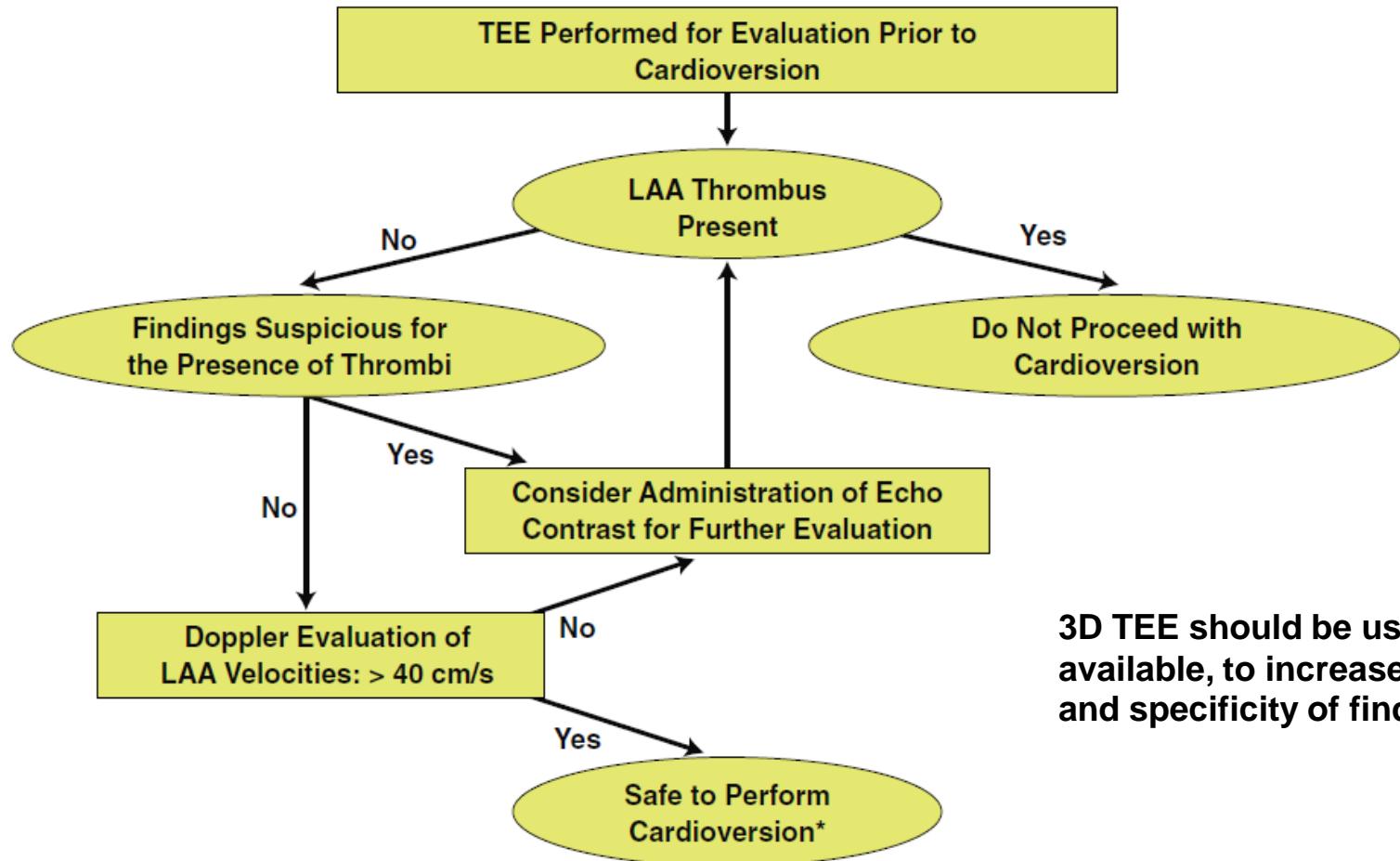
## A Meta-analysis



Best results obtained with late phase imaging

Romero, J. et al. *Circ. Cardiovasc. Imaging* 6, 185–194, (2013).

# Schematic Approach for TEE Evaluation of the LAA Before Cardioversion



3D TEE should be used, if available, to increase sensitivity and specificity of findings

Beigel R, et al. J Am Coll Cardiol Img 2014;7:1251–65

# Areas of Current Research Interest

- Relationship between atrial fibrosis, atrial cardiomyopathy, and indices of LA stasis
- Predictive value of measures of LA stasis (strain/speckle mapping, left atrial size and contractility, spontaneous echo contrast) for spontaneous ischemic stroke, or stroke complications from interventional procedures within the LA – ablation, mitra clip, ASD occlusion etc.
- Combination of stasis, endothelial abnormalities and hypercoagulability issues for stroke prevention, in comparison with clinical risk stratifiers/biomarkers
- Value of left atrial appendage excision, occlusion for stroke prevention
- Predictive value of LAA /stasis risk based on LAA morphology
- Improved techniques for assessing stasis

# LAA and Stasis: Key Points

- An estimated 47% of thrombi in valvular atrial fibrillation (AF) and **91% of thrombi in nonvalvular AF are localized in the left atrial appendage** (LAA)
- **LAA flow stasis (or spontaneous echocardiographic contrast; SEC)** is a pattern of blood flow (echogenicity) attributed to ultrasonic backscatter from blood cell aggregates that form under low shear conditions
- **SEC** is formed through protein-mediated (particularly fibrinogen) red cell aggregation promoting red cell rouleaux formation, and is the **cardiac factor most-strongly associated with LAA thrombus formation**
- **Transoesophageal echocardiography is the gold standard** for the evaluation of LAA stasis and thrombosis, and promising results have been reported for intracardiac echocardiography and transthoracic echocardiography with contrast
- **Cardiac CT** is an accurate, noninvasive imaging modality for the detection of LAA thrombi, particularly when delayed imaging acquisition protocols are used; CMR – not useful