ECG/Imaging Modalities for Stroke Risk Stratification in Patients with Atrial Fibrillation

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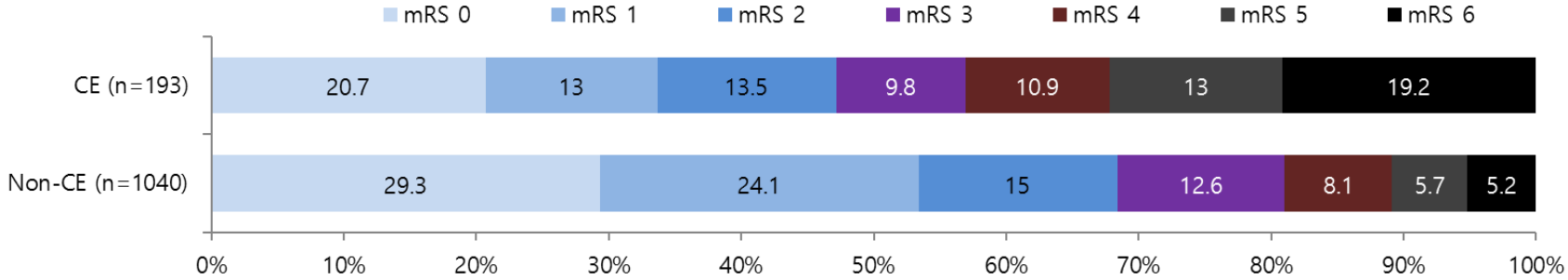
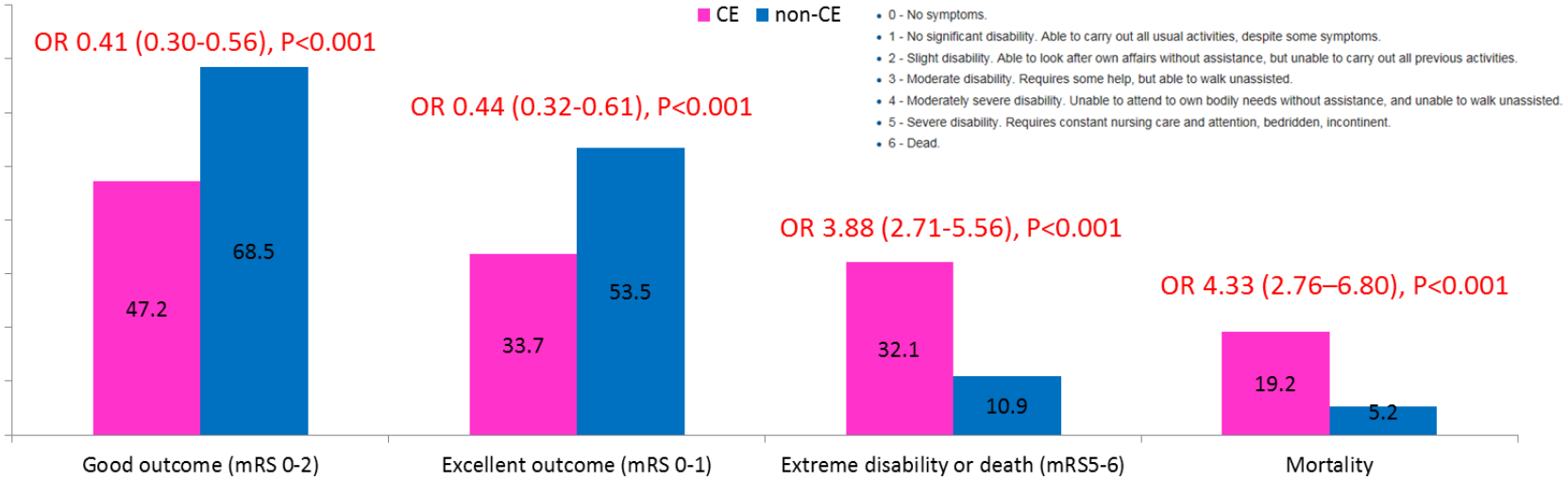
Agenda

1. ECG abnormalities and stroke incidence
2. LA remodeling and stroke in AF
3. Imaging of LAA for risk stratification of stroke
4. Emerging technique in intracardiac flow dynamics

AF-related stroke causes greater diability

- **AF-related strokes usually present with severe strokes.**
  - **higher bed-ridden presentation (41% vs. 24%)[1]**
  - **Higher 30-day post-stroke mortality (25% vs 14%)[2]**





Dulli DA et al. Neuroepidemiology. 2003 Mar-Apr;22(2):118-23
Lin HJ et al. Stroke. 1996 Oct;27(10):1760-4.
Hong KS et al,. J Stroke Cerebrovasc Dis. 2013 22(8):e373-80

How can we improve stroke prediction?

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

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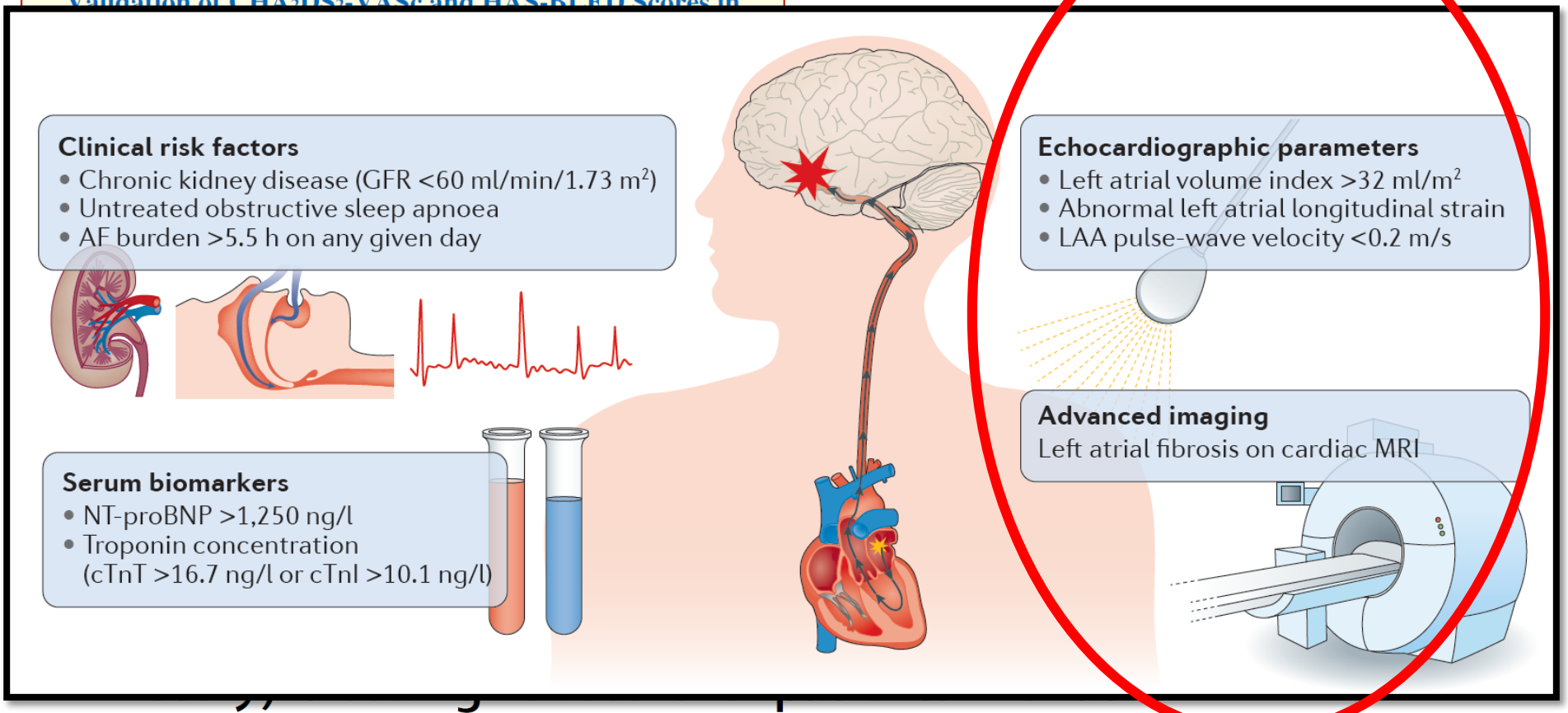
Validation of CHA$_2$DS$_2$-VASc and HAS-BLED Scores in



fibrillation: a derivation and validation study

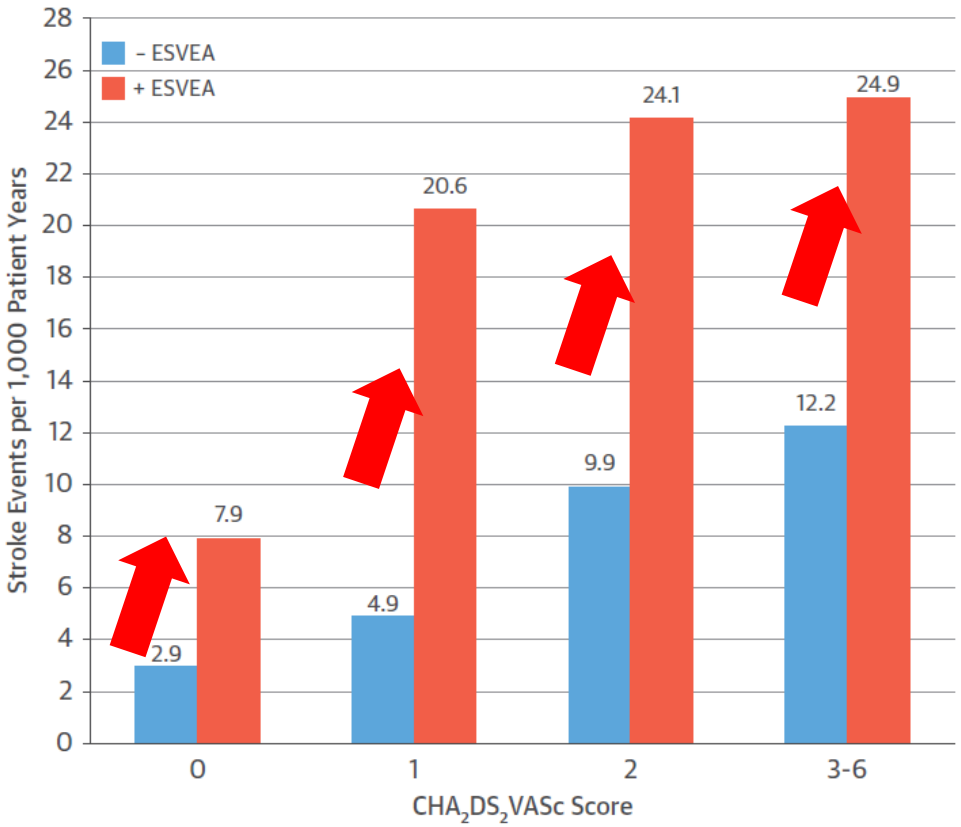
Ziad Hijazi, Jonas Oldgren, Johan Lindbäck, John H Alexander, Stuart J Connolly, John W Eikelboom, Michael D Ezekowitz, Claes Held, Elaine M Hylek, Renato D Lopes, Agneta Siegbahn, Salim Yusuf, Christopher B Granger, Lars Wallentin, on behalf of the ARISTOTLE and RE-LY Investigators

Ambulatory Holter monitoring in evaluation of silent/asymptomatic atrial tachyarrhythmias in high-risk populations

- **Larsen et al. Copenhagen Holter Study**
  - **678 subjects w/o CVD/AF, 55-75 yrs.**
  - **14.4 years follow up, 48-h Holter**
  - **ESVEA(+): 14.6%, HR=1.96 for ischemic stroke, p=0.02**
- **Engstrom et al. 'men born in 1914'**
  - **402 men, 68 y, 24-h Holter**
  - **APC>218/24hr: HR 1.9 for stroke, p=0.04**

Excessive Atrial Ectopy and Short Atrial Runs Increase the Risk of Stroke Beyond Incident Atrial Fibrillation

FIGURE 1 Incidence of Stroke per 1,000 Patient-Years According to ESVEA and CHA_2DS_2-VASc score

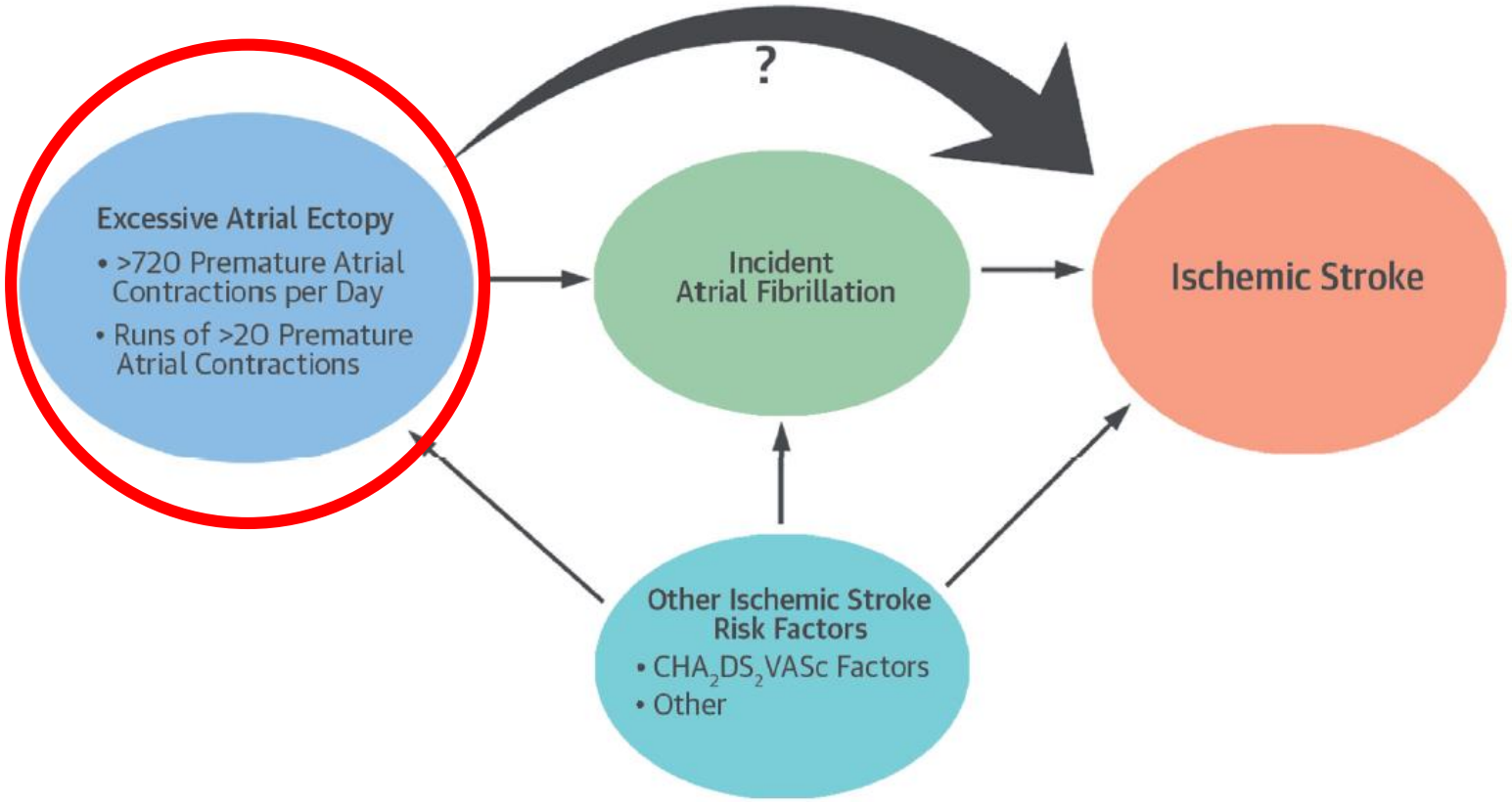


Relationship between ESVEA & stroke remained significant despite of..

- Censoring at the time of AF
- Multivariate adjustment with AF as a time-varying exposure
- Fine-Gray Competintg risk model with AF & death as competing risk.

J Am Coll Cardiol 2015;66:232–41

Excessive Atrial Ectopy and Short Atrial Runs Increase the Risk of Stroke Beyond Incident Atrial Fibrillation



Excessive atrial ectopy and short atrial runs are associated with an increased risk of ischemic stroke beyond atrial fibrillation. However, the exact mechanism is not known and may be caused by undiscovered incident atrial fibrillation or an increased vascular risk profile.

J Am Coll Cardiol 2015;66:232–41

Recommendation in consensus document

- **Excessive supraventricular ectopic activity (ESVEA): 30 premature supraventricular contractions (PSC) /hour (≥720 PCS /24 hours) or episode of PSC runs ≥20 beats.**

ESVEA documented by Holter monitoring can be considered as a surrogate marker for paroxysmal AF.

ESC European Society of Cardiology

Europace (2017) 19, 1556–1578
doi:10.1093/europace/eux163

EHRA CONSENSUS DOCUMENT

Device-detected subclinical atrial tachyarrhythmias: definition, implications and management—an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE)

Device detected AHRE & thromboembolic risk

- **TRENDS study**
  - **Prospective, observational**
  - **2486 pts**
  - **One or more stroke risk factor**
  - **PM or ICD**
  - **AT/AF burden was defined as the maximum number of hours of AT/AF on any day during the antecedent 30 days and may have included more than 1 episode of AT/AF on that day**
  - **Detection: >175 bpm, ≥20 sec.**

Circ Arrhythmia Electrophysiol. 2009;2:474-480.

- **AT/AF burden was divided into 3 subsets**
  - **Zero AT/AF burden,**
  - **Low AT/AF burden (<5.5 h)**
  - **High AT/AF burden (≥5.5 h at least 1 day)**
  - **Cut off was medial value of AF burden**
  - **No EGM**

Table 2. TE Rates for the Overall Study Group (Unadjusted)

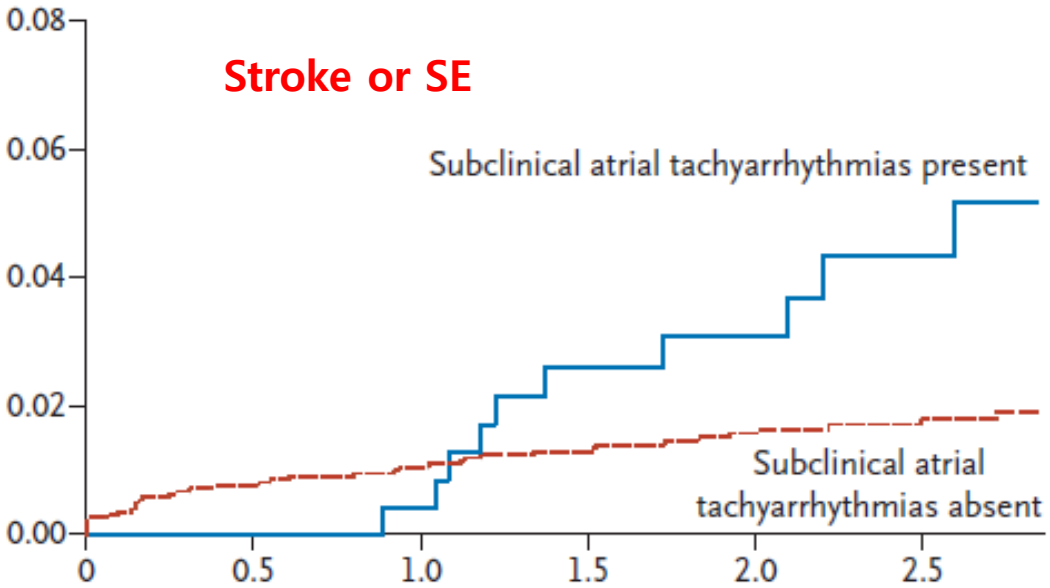
AT/AF Burden Subset	Annualized TE Rate (95% CI), %	Annualized TE Rate Excluding TIAs (95% CI), %
Zero AT/AF burden	1.1 (0.8–1.6)	0.5 (0.3–0.9)
Low AT/AF burden (<5.5 h)	1.1 (0.4–2.8)	1.1 (0.4–2.8)
High AT/AF burden (5.5 h)	2.4 (1.2–4.5)	1.8 (0.9–3.8)

HR 2.2 (0.96-5.05, P=0.06)

Circ Arrhythmia Electrophysiol. 2009;2:474-480.

Subclinical Atrial Fibrillation and the Risk of Stroke

- **ASSERT**
- **2580 pts, ≥65 years, No AF Hx. 2.5 year-f/u.**
- **AHRE: ≥190 bpm, >6 min.**
- **AHRE occurred 10% in 3 month.**
- **HR=3.9 in CHADS score >2 and 3 month-AHRE(+) group**



AHRE in 3 months after inclusion
Vs.
No AHRE in 3 months

N Engl J Med 2012;366:120-9.

Stroke risk of SCAF was generally lower than clinical AF

Table 3. Risk of Ischemic Stroke or Systemic Embolism after the 3-Month Visit, According to Baseline $CHADS_2$ Score and According to Whether Subclinical Atrial Tachyarrhythmias Were or Were Not Detected between Enrollment and the 3-Month Visit.

$CHADS_2$ Score	No. of Patients	Subclinical Atrial Tachyarrhythmias between Enrollment and 3 Months						Hazard Ratio for Ischemic Stroke or Systemic Embolism with Subclinical Atrial Tachyarrhythmias (95% CI)*
		Present			Absent			
		no. of patients	*no. of events*	*%/yr*	*no. of patients*	*no. of events*	*%/yr*	
1	600	68	1	0.56	532	4	0.28	2.11 (0.23–18.9)
2	1129	119	4	1.29	1010	18	0.70	1.83 (0.62–5.40)
>2	848	72	6	3.78	776	18	0.97	3.93 (1.55–9.95)

N Engl J Med 2012;366:120-9.

Silent AF related to silent brain ischemia

- **109 pts**
- **AHRE> 5 min.**
- **AHRE was found in 25% of pts.**
- **AHRE independently prectied silent ischemic lesion on brain CT performed at inclusion**

Europace (2015) 17, 364–369

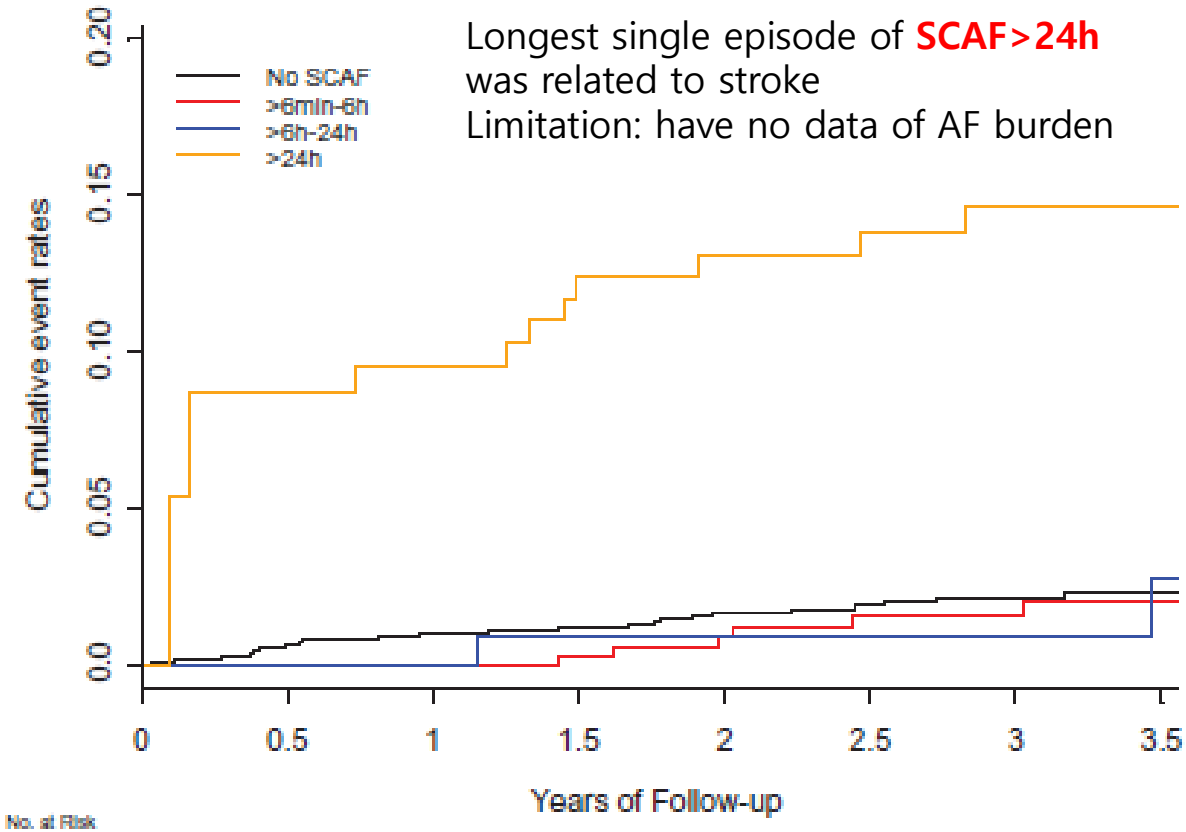
Thromboembolic risk of AF in patients with CIED

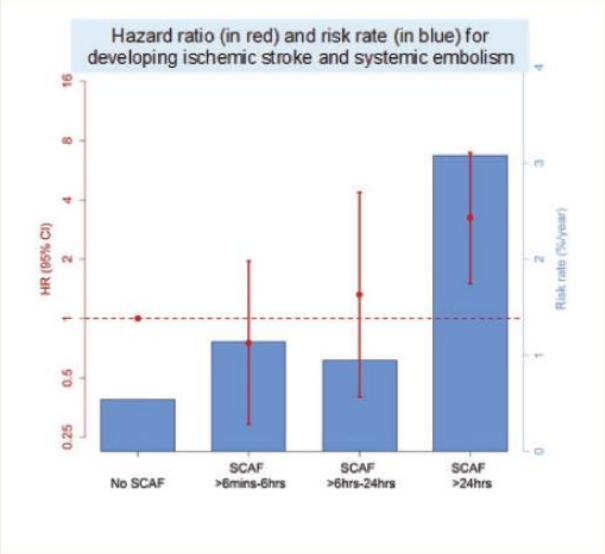
Year	Study	Number	F/U	Rate cut-off	Duration cut-off	HR	Event rate
2003	MOST	312	27 months	>220 bpm	5 min	6.7	5% vs. 1.3%
2005	Italian AT500 registry	725	22 months	>174 bpm	24 hour	3.1	Annual 1.2%
2009	Botto et al.	568	1 year	>174 bpm	CHADS+ burden		Overall 2.5%
2009	TRENDS	2486	1.4 years	>175 bpm	5.5 h	2.2	2.4% vs. 1.1%
2012	Home Monitor CRT	560	370 days	>180 bpm	3.8 h	9.4	Overall 2.0%
2012	ASSERT	2580	2.5 years	>190 bpm	6 min	2.5	1.69% vs 0.69%
2014	SOS AF	10016	2 years	>175 bpm	1 h	2.11	Annual 0.39%

There is still uncertainty regarding the duration of device-detected AF that increases TE risk.

Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT

Isabelle C. Van Gelder[1]*, Jeff S. Healey[2], Harry J.G.M. Crijns[3], Jia Wang[2],





Summarizing Figure SCAF >24 h is associated with comparable risk of ischemic stroke and systemic embolism as clinical AF. In this figure the hazard ratio from time dependent Cox model (long term effect, red) and the risk rate from the landmark analysis (blue) of ischemic stroke and systemic embolism are depicted.

without SCAF.

Eur Heart J. 2017 May 1;38(17):1339-1344

Recommendations (2017 consensus)

- For patients with two additional CHA2DS2-VASc risk factors (≥2 in males, ≥3 in females) oral anticoagulation is recommended for AF burden >5.5 h/day (TRENDS)
- AHRE> 5 min may merit OAC if multiple risk factors are present. (MOST, ASSERT)

ESC European Society of Cardiology

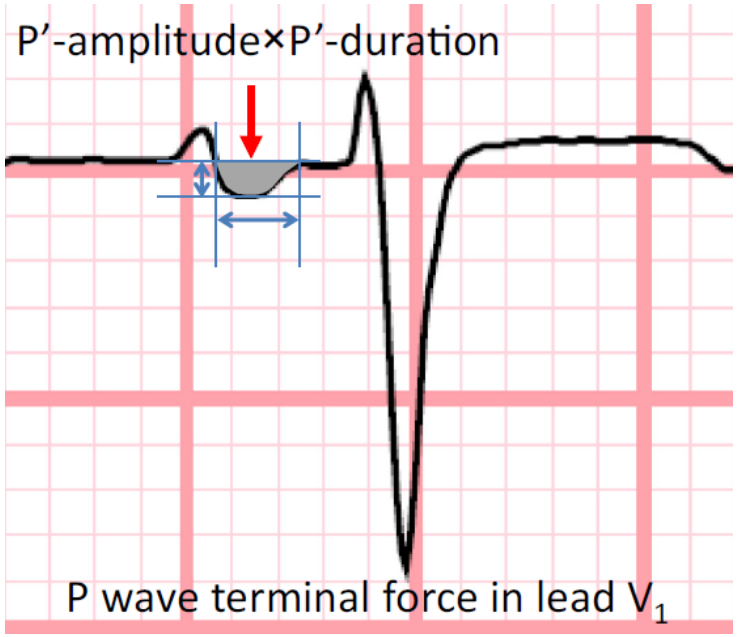
Europace (2017) 19, 1556–1578
doi:10.1093/europace/eux163

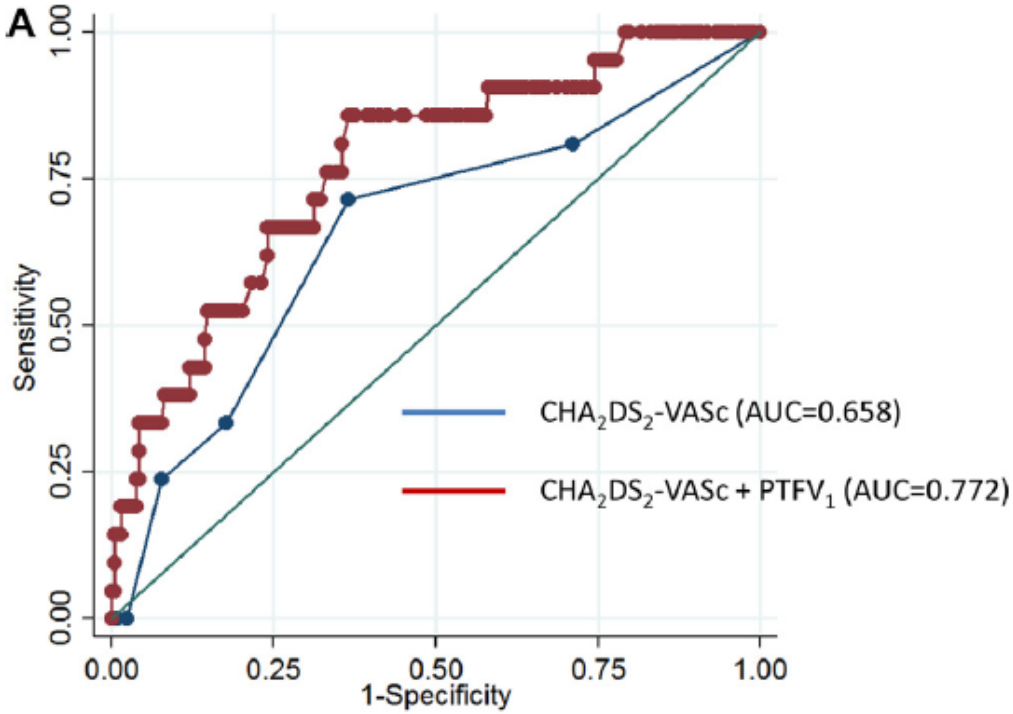
EHRA CONSENSUS DOCUMENT

Device-detected subclinical atrial tachyarrhythmias: definition, implications and management—an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE)

P wave morphology in simple ECG

Area of terminal inverted P portion independently predicted ischemic stroke.
Had an incremental value in addition to CHADSVASc score.





Am J Cardiol 2018;122:242-247

P wave signal-averaged ECG for AF/stroke risk evaluation

68 pts, post stroke, no AF.

Presence of atrial late potential (risk ratio 11.15; p = 0.002) and frequent PACs (>100/24 h) (risk ratio 4.53; p = 0.007) had significant correlation to the occurrence of AF.

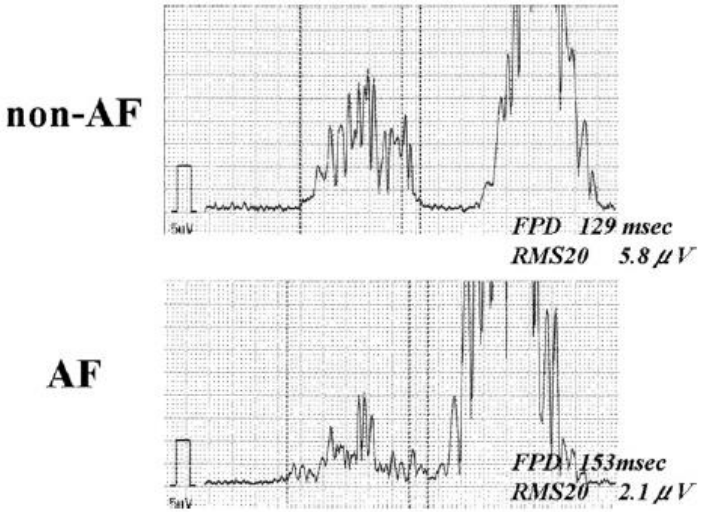


Fig. 1. Representative P-wave signal-averaged electrocardiography in each group. It is notable that the filtered P-wave duration (FPD) is longer and the root-mean-square voltage for the last 20 ms (RMS20) is lower in the atrial fibrillation (AF) patient than in the non-AF patient.

Table 2
Multivariate Cox proportional hazard analysis for the identification of patients at risk for AF.

	p-Value	Hazard ratio (95% CI)
Age ≥ 70 (years)	0.188	2.06 (0.7–6.1)
ALP	0.002	11.15 (2.5–49.7)
PAC > 100 (beats/day)	0.007	4.53 (1.5–13.6)
LAD ≥ 41 (mm)	0.111	2.29 (0.8–6.3)
BNP ≥ 80 (pg/ml)	0.557	1.36 (0.5–3.8)

AF, atrial fibrillation; ALP, atrial late potentials; BNP, brain natriuretic peptide; CI, confidence interval; LAD, left atrial dimension; PAC, premature atrial contractions.

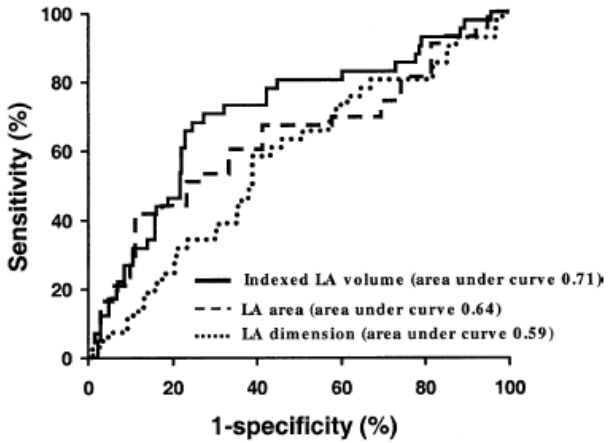
Journal of Cardiology 61 (2013) 49–52

LA imaging and stroke risk

- **LA volume shows stronger association with CV outcome than LA diameter (d/t asymetrical remodeling?)**
- **Marker of diastolic dysfunction, LA pressure elevation.**
- **Associated with**
  - **Incidence of AF**
  - **Stroke**
  - **Overall mortality (after MI)**
  - **Death and hospitalization (DCMP)**

317 pts, NSR at baseline, 3.5 yrs f/u

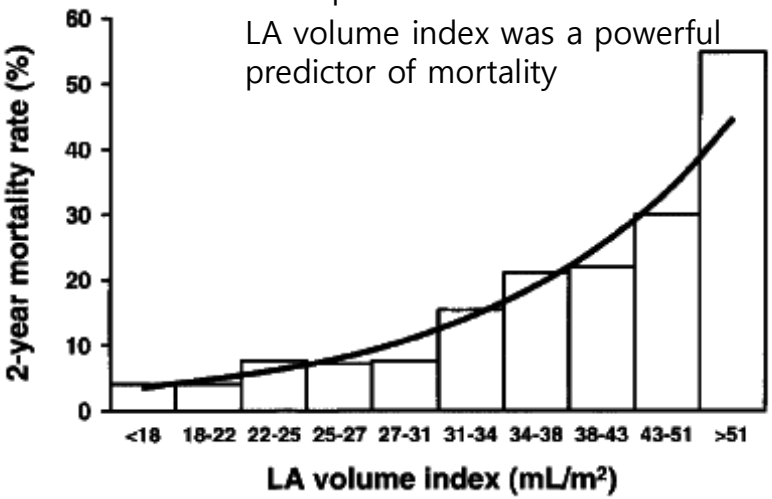
LAVI predicted MACE (AUC=0.71)



J Am Coll Cardiol 2006;47:1018–23

>300 patients with AMI

LA volume index was a powerful predictor of mortality



Moller et al. Circulation. 2003;107:2207-2212.

Prediction of AF by LA volume & function in normal population

AF-risk being highest for subjects with concomitant LA emptying fractions <49% and LA volume >38 ml/m^2 (hazard ratio 9.3, p=0.003)

574 subjects with NSR, mean 74 yrs old, 2 yr f/u

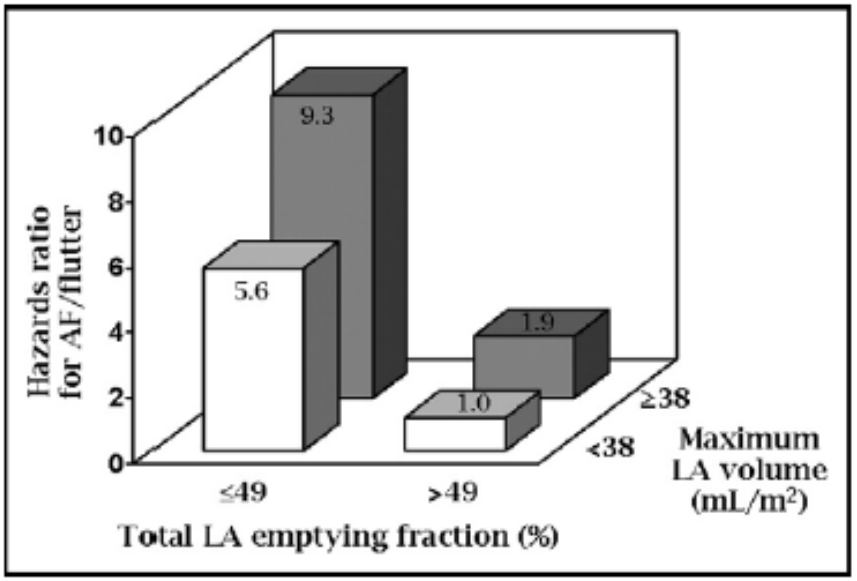


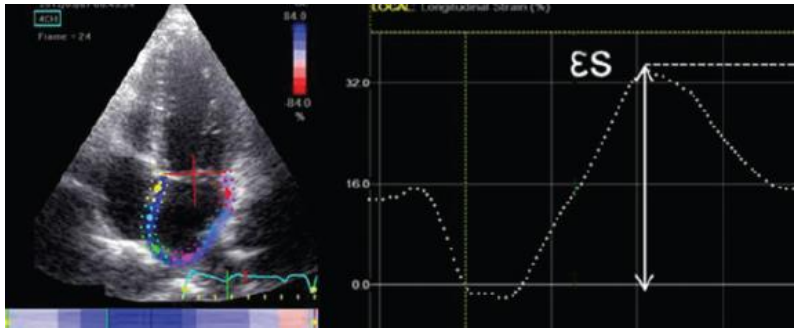
Figure 3. Age-adjusted associations between LA emptying fraction and indexed maximum LA volume for the prediction of AF or atrial flutter.

Am J Cardiol 2008;101:1626 –1629

Prediction of AF by strain after CVA

Of 538 patients, 61 (11%) developed AF, and this occurred within 2 years in 85% of patients.

with a 13-fold greater hazard of AF ($p < 0.001$) in patients with increased clinical risk and reduced reservoir strain (AUC=0.85)



Peak positive longitudinal strain (reservoir)

TABLE 2 AUC for ROC Analysis of Echocardiographic Variables

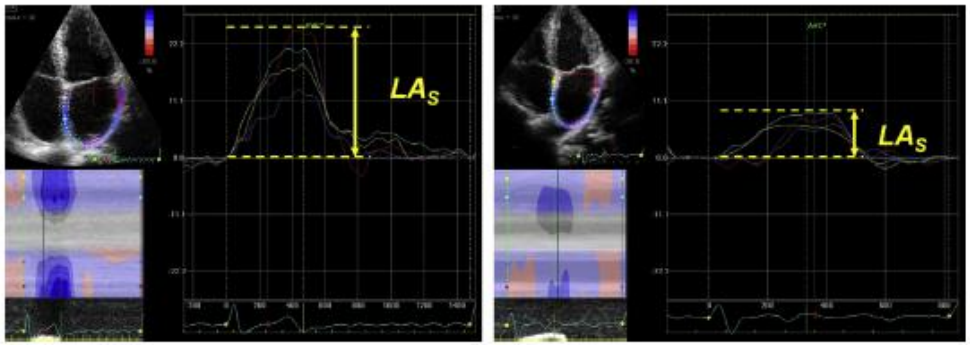
TTE Parameter	AUC	p Value
εR	0.849	<0.001
εCt	0.825	<0.001
εCd	0.759	<0.001
E/e'	0.661	<0.001
Average e'	0.653	<0.001
LA volume, ml/m^2	0.646	<0.001

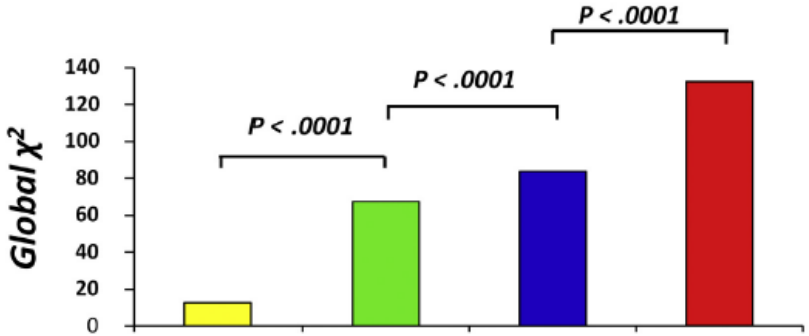
F Pathan et al. J Am Coll Cardiol Img 2018;11:1557–65

Prediction of stroke by LA strain

Left Atrial Strain Provides Incremental Value for Embolism Risk Stratification over CHA2DS2-VASc Score
AF with systemic embolism(82), Japanese
AF without embolism(204)
Cut off: Global LA strain <12%

Control **Stroke**



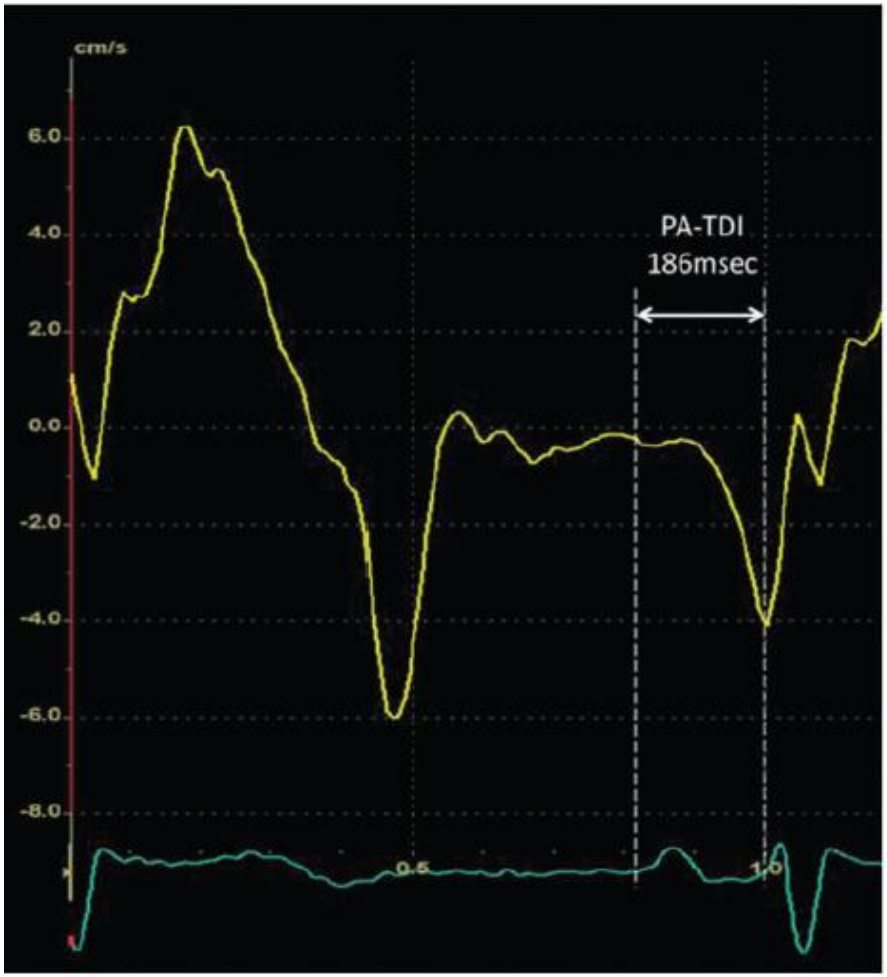


Models	Model 1 (χ2 12.8)	Model 2 (χ2 67.4)	Model 3 (χ2 83.9)	Model 4 (χ2 132.4)
Variable	CHA_2DS_2-VASc score	+ OAC use	+ LA emptying fraction	+ Global LA_S
CHA_2DS_2-VASc score	1.35 (1.14-1.61) *P* < .001	1.47 (1.21-1.79) *P* < .001	1.45 (1.19-1.76) *P* < .001	1.11 (0.88-1.40) *P* = .362
OAC use	-	0.12 (0.06-0.22) *P* < .001	0.12 (0.06-0.23) *P* < .001	0.10 (0.05-0.21) *P* < .001
LA emptying fraction	-	-	0.95 (0.92-0.98) *P* < .001	0.98 (0.95-1.01) *P* = .151
Global LA_S	-	-	-	0.75 (0.68-0.83) *P* < .001

Decreased LASp and LASRr were independently associated with stroke in patients with permanent AF.
(J Am Soc Echocardiogr 2011;24:513-9.)

J Am Soc Echocardiogr 2014;27:709-16.

Prediction of stroke by LA imaging (2)



PA-TDI:

Distance from

P wave to A' wave

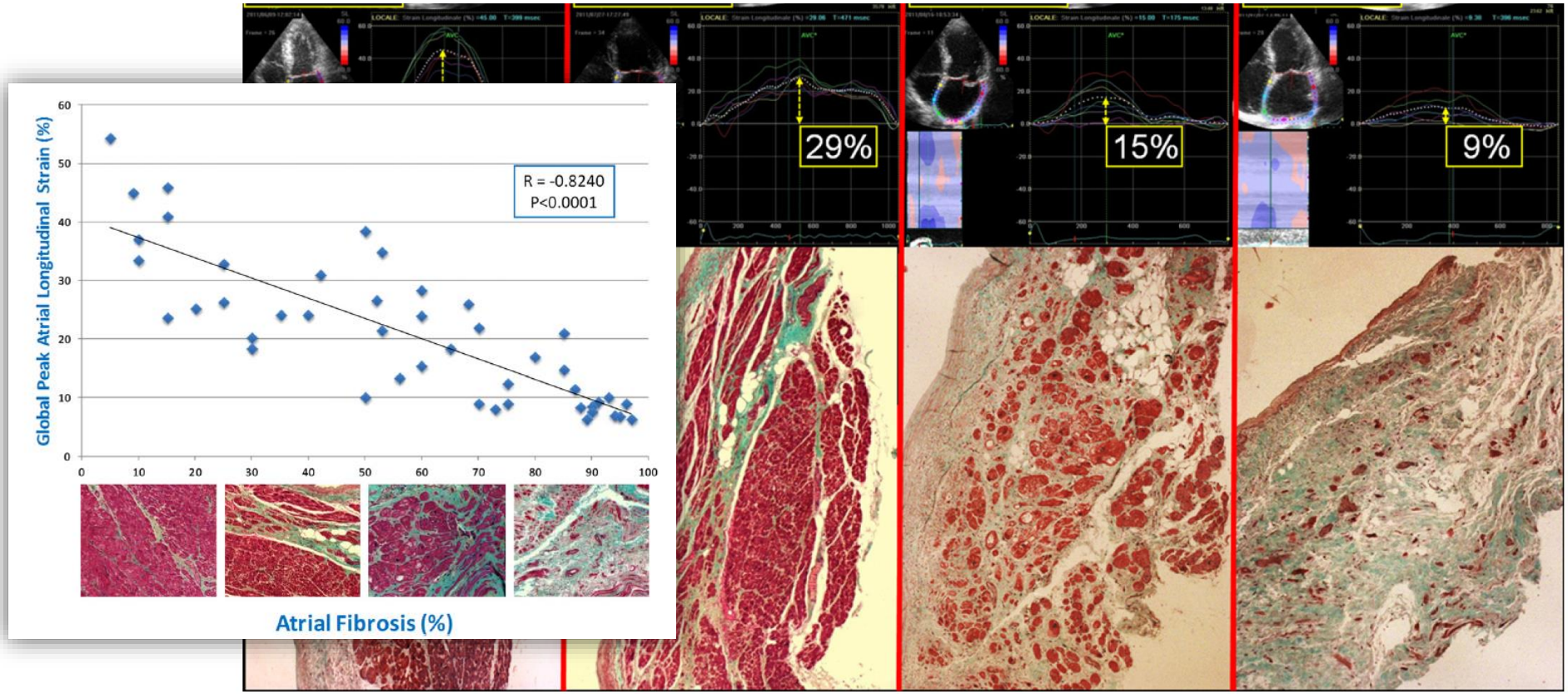
=electro-mechanical delay

>1300 pts, 7.9 yrs f/u
LA reservoir strain & PA-TDI provides additional risk stratification for stroke

European Heart Journal (2018) 39, 1416–1425

LA strain correlated with fibrosis

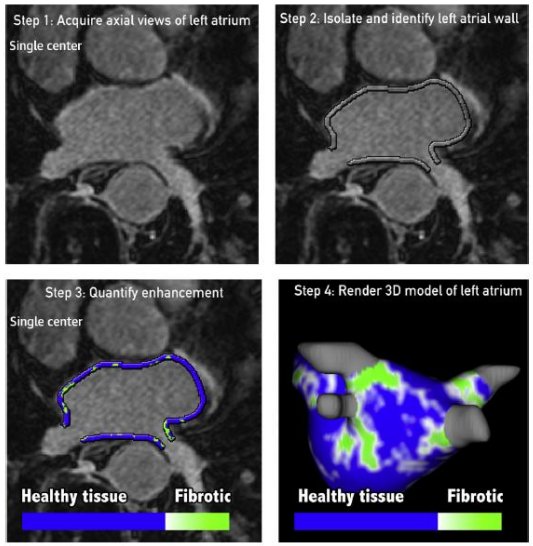
Global PALS showed the best diagnostic accuracy to detect LA fibrosis (area under the curve 0.89) than LAVI, LAEF, E/E' (46 pts, OP for MR)



Am J Cardiol 2013;111:595e601

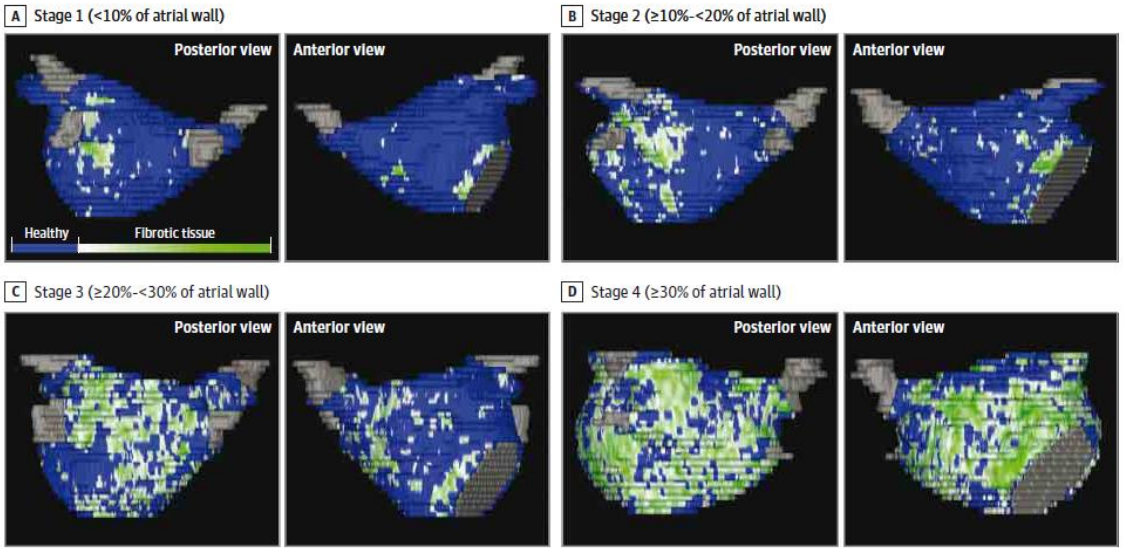
LA Fibrosis Assessment From LGE-MRI

Steps to identify LA fibrosis



J Am Coll Cardiol EP 2017;3:791–802

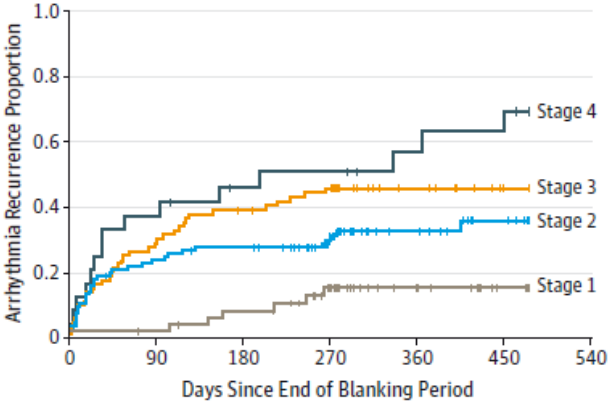
Stage 1~4 fibrosis (Utah group)



272 of 329 pts

(57 pts (17%) exluded d/t poor MRI quality)

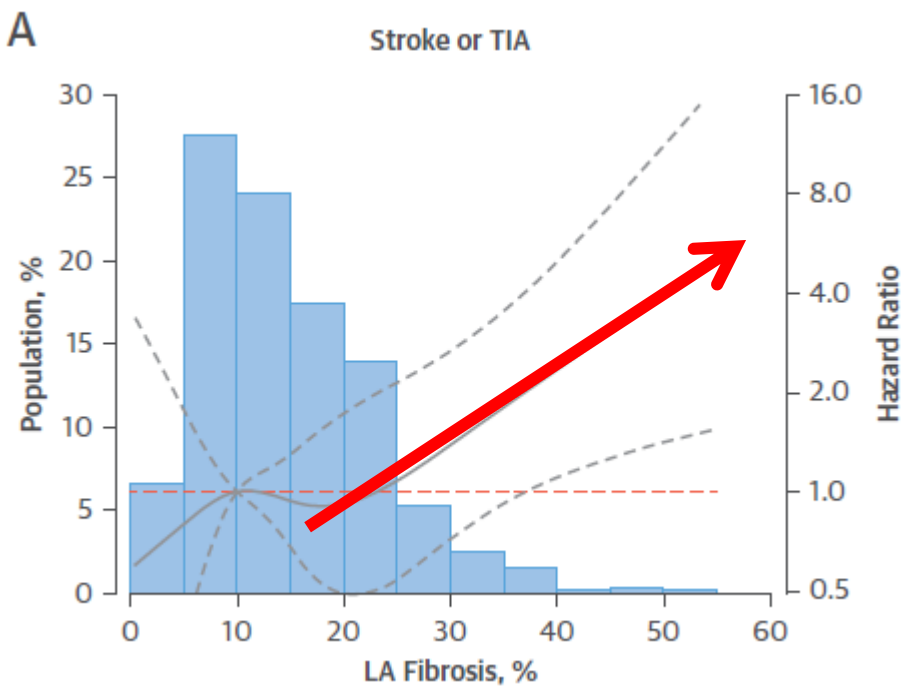
The addition of fibrosis to a recurrence prediction model → C statistic increasing from 0.65 to 0.69

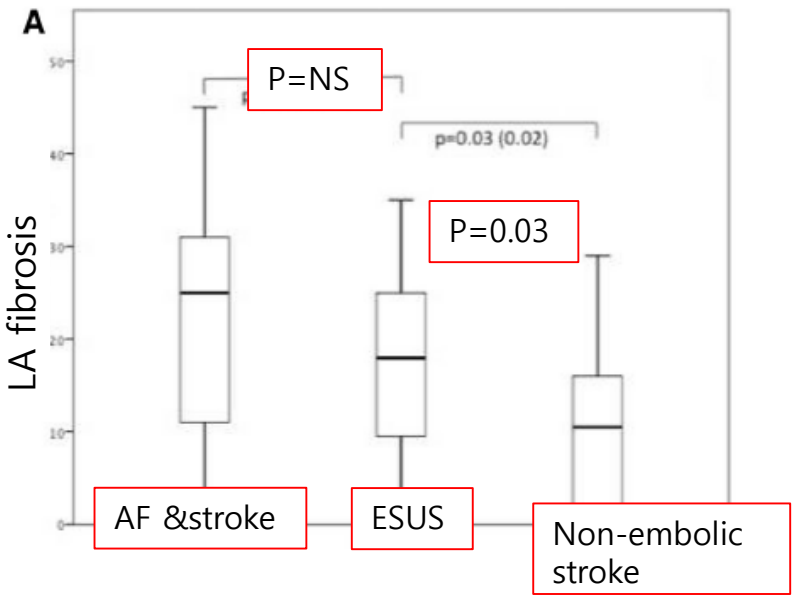


DECAAF . 2014 JAMA

LA fibrosis and stroke risk

1,228 pts with AF.
62 stroke or TIA
Retrospective.
LA fibrosis well correlated with stroke



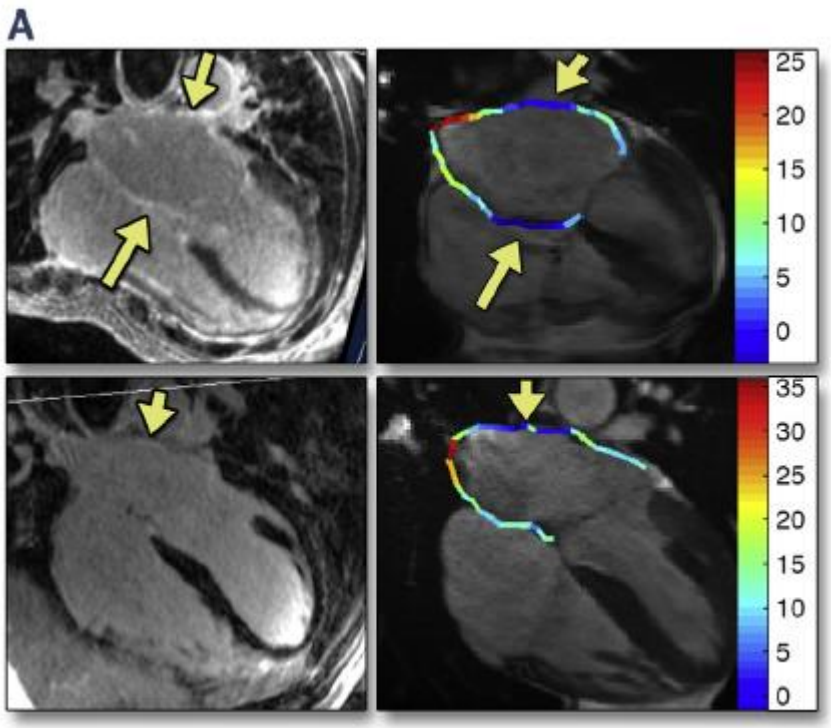


- Total 111 pts.
- ESUS a higher LA fibrosis (p=0.03)
- AF and ESUS showed a similar value of atrial fibrosis.
- an atrial disease may be associated with stroke.

J Am Coll Cardiol 2017;70:1311 - 21

Stroke. 2018;49:734–737

Value of cardiac MRI in stroke prediction



Low strain region = LA fibrosis region

JACC 2017′ letter. http://dx.doi.org/10.1016/j.jcmg.2016.01.015

169 PAF pts.

LA strain measured by MRI had additive value in stroke prediction.

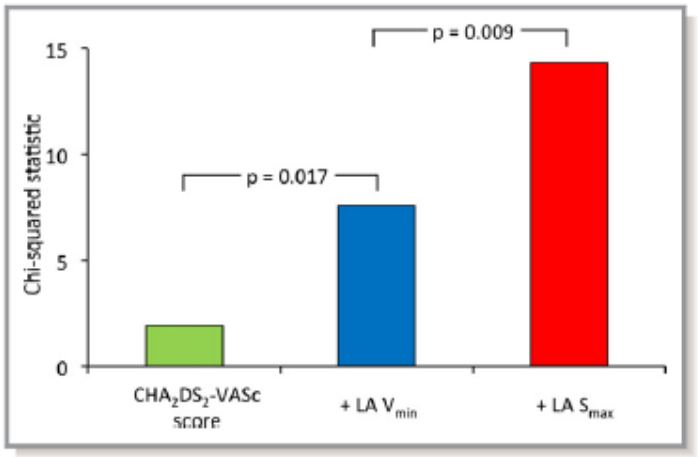
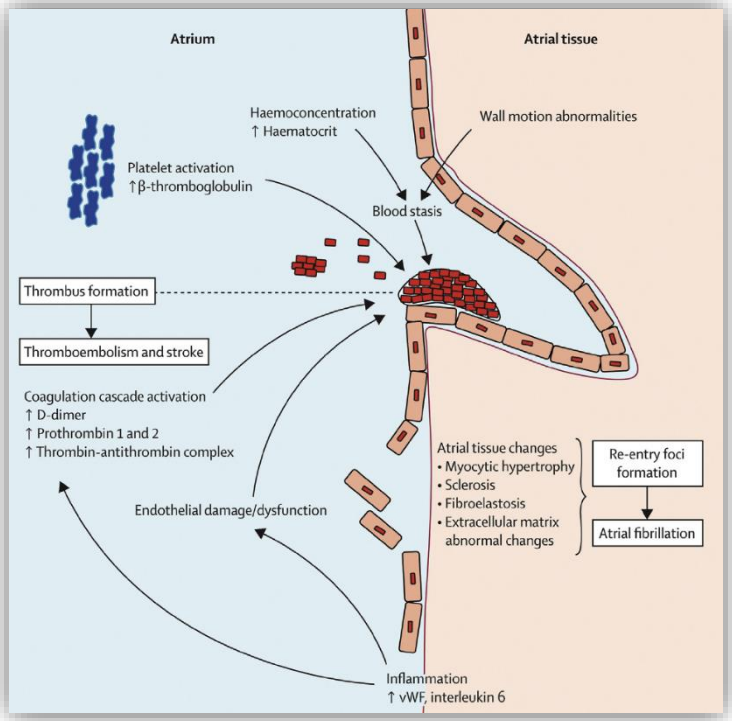


Figure 4. Incremental value of left atrial (LA) strain for diagnosis of stroke. The addition of the LA minimum volume (V_{min}) to the model on the basis of the CHA_2DS_2-VASc score resulted in significant improvement in the diagnostic value for stroke. The value was further increased by adding the LA global longitudinal maximum strain (S_{max}).

J Am Heart Assoc. 2015;4:e001844

LAA as a more important embolic source in NVAF

- **20% of ischemic stroke has cardiac embolic source**
- **AF is most common cardiac abnormality associated with stroke**
- **NVAF with stroke : ~90% have LAA thrombus**
- **57% of thrombi in rheumatic heart disease**



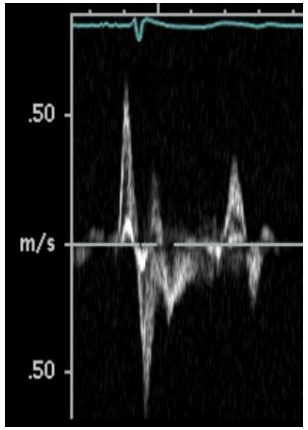
Blackshear JL, Odell JA. Ann Thorac Surg 1996;61(2):755–9.

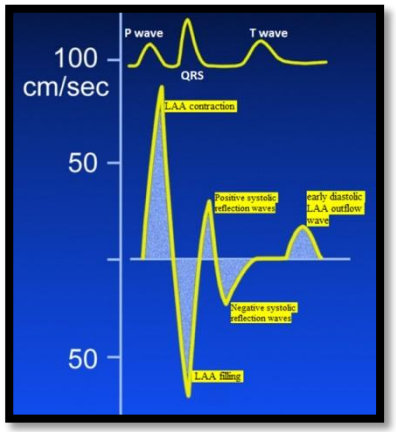
Imaging of LAA and stroke risk

1. Spontaneous echocontrast/thrombus
2. LAA peak emptying velocity
3. LAA orifice size/LAA volume
4. LAA morphologic type/trabeculation
5. Flow pattern of LAA

LAA flow in NSR vs. AF

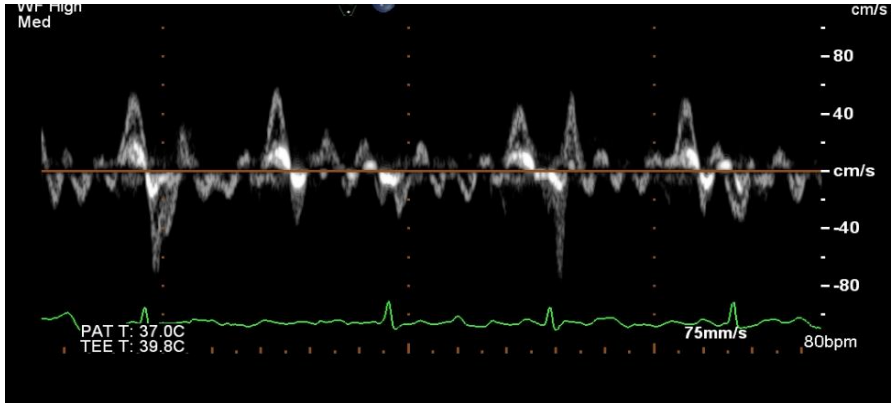
NSR



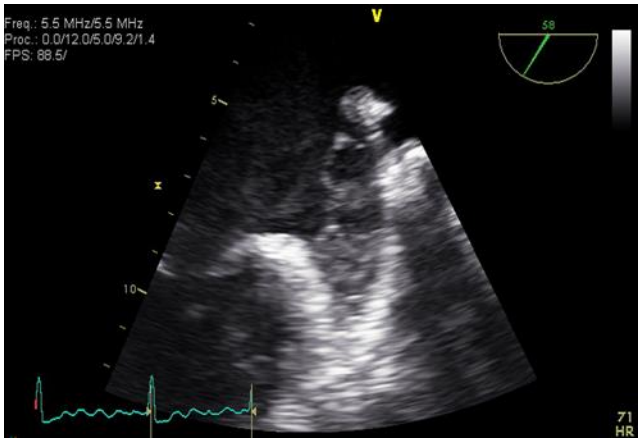


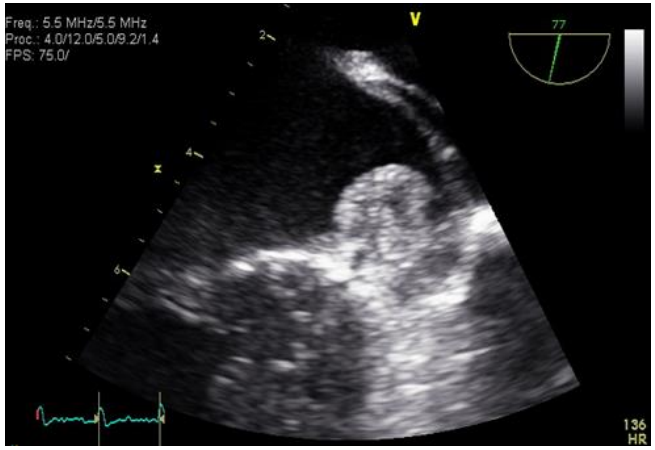
Late diastolic contraction flow

AF



Decreased LAA flow → Spontaneous echocontrast/thrombus → increased stroke



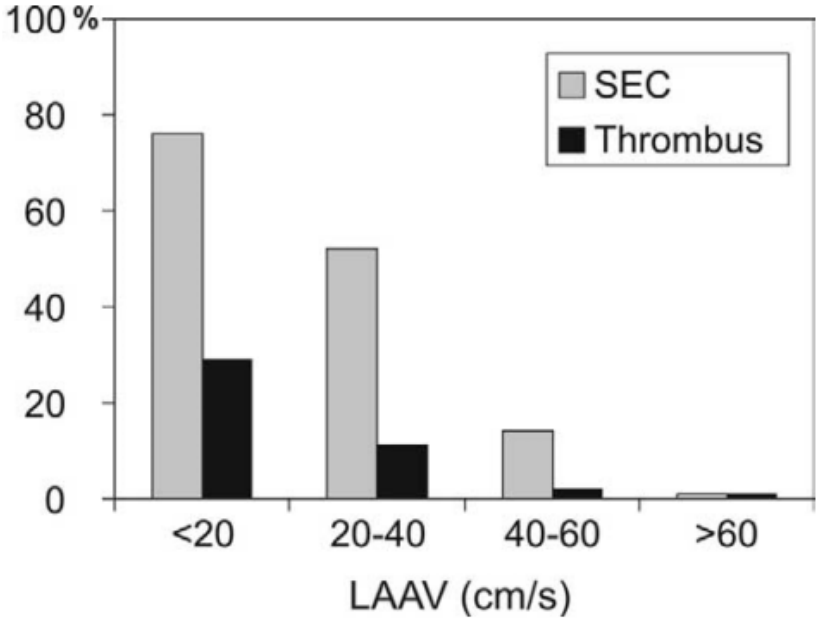


J Am Coll Cardiol. 1988 Jun;11(6):1204-11.

Decreased LAA peak velocity and SEC/thrombus/stroke

A lot of observation data demonstrated the association between low LAA velocity and SEC/thrombus/stroke

- **Various cut off value**
- **SEC increased when LAAV<35 cm/s**
  - **(J Am Coll Cardiol 1994;23:961-9)**
- **Thrombus/SEC increased significantly at an LAAV < 55 cm/s**
  (JASE 2005;18:1366-72)
- **LAA peak velocity<20 cm/s**
  - **RR 1.7 for stroke**
  - SPAF III data, J Am Coll Cardiol 1998;31:1622–6
  - **OR 4.48 for stroke in age <70**
  - CHEST 2001; 120:840 - 846



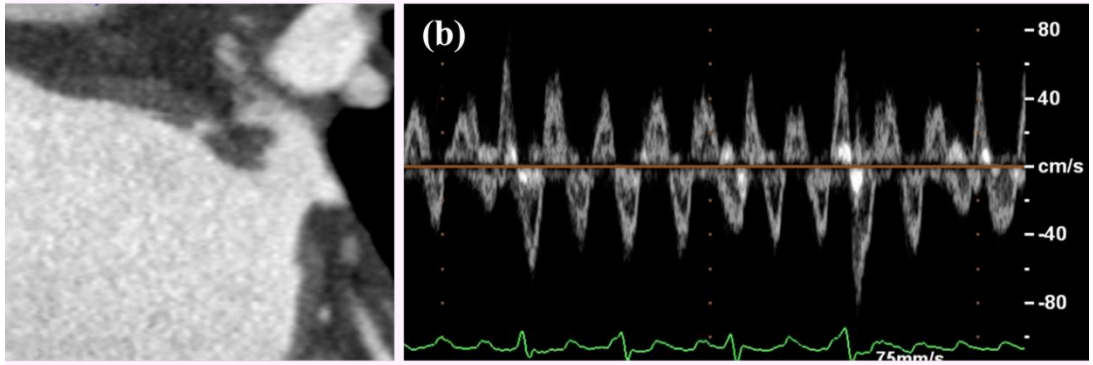
LAA size and stroke

- **Longer duration of AF → enlarged LAA**

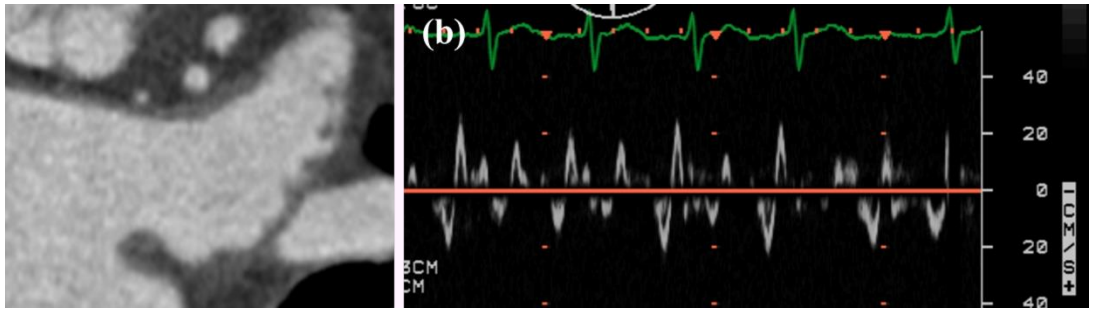
- **Larger LAA → thrombus/stroke**
  - **LAA area by TEE** (circulation 1991;84:223-231)
  - **CT/MRI: LAA orifice size/depth/volume was associated to stroke** (JCE 2011;22:10-15)
    - **OR:LAA os size>>depth>volume in this study.**

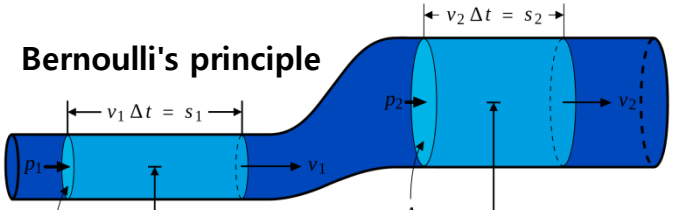
Relationship between LAA orifice size and emptying flow velocity

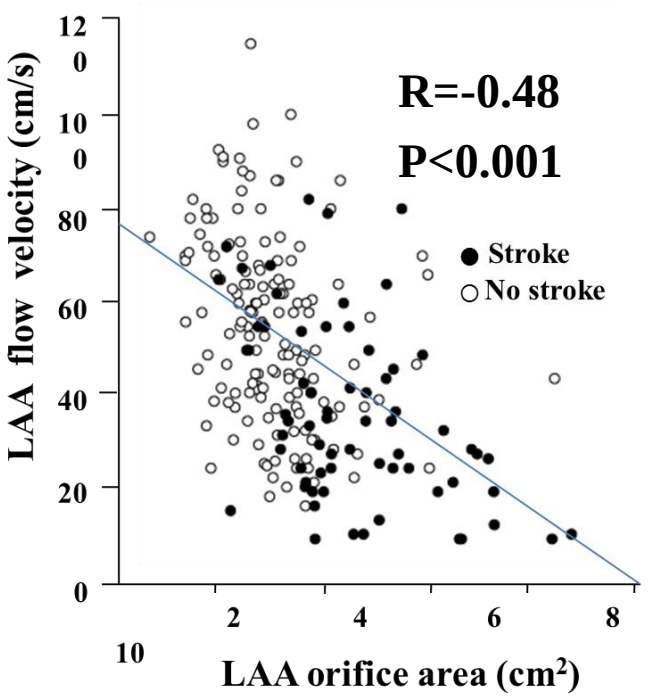
Small LAA with preserved LAA velocity



Large LAA with decreased LAA velocity



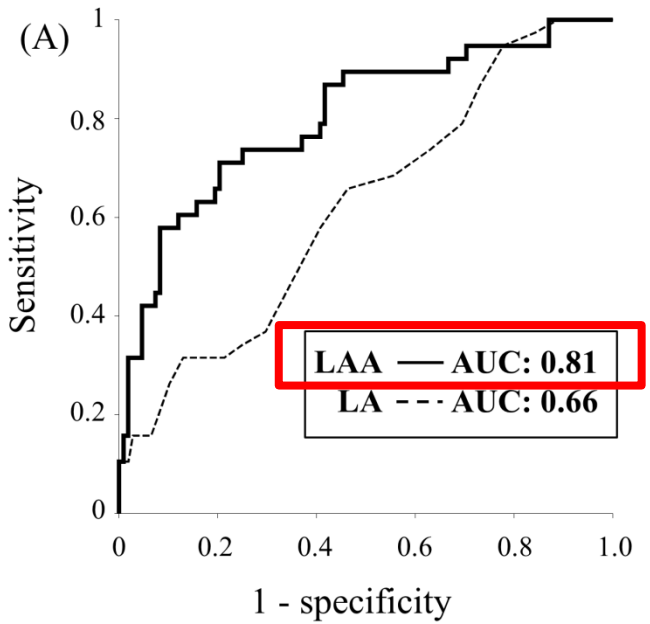




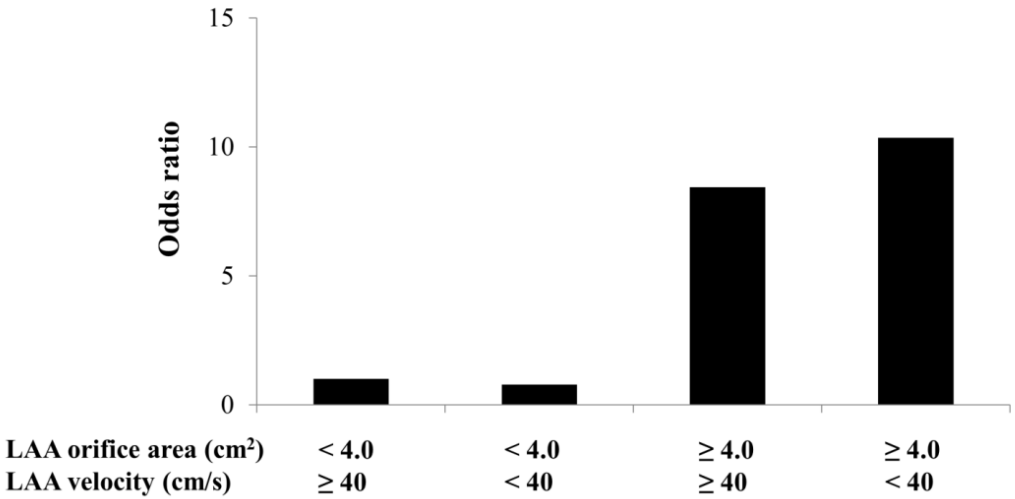
Lee JM, Joung B et al. Am J Cardiol 2014 Mar 25;113(6):963-9

Additional value of LAA for Stroke prevention in low risk patients (CHA_2DS_2VASc <2)

LAA orifice size has the largest AUC

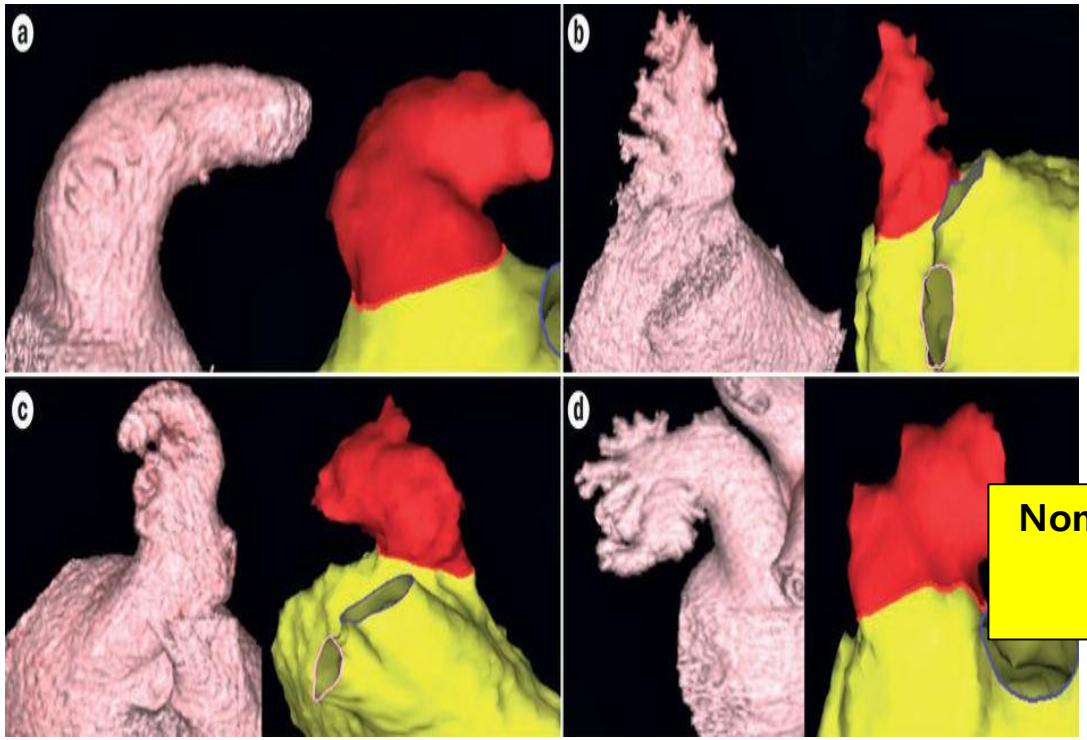


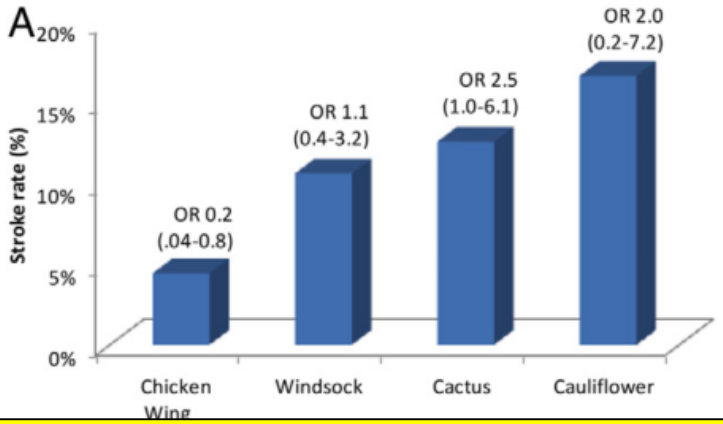
Patients with both large LAA os and low LAA velocity showed very high odds ratio of stroke (OR 10.9, 95% CI 3.0-40.0, p<0.001)



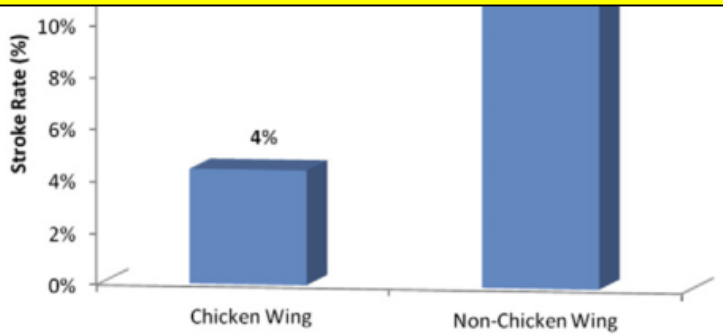
Lee JM, Joung B et al. Heart Rhythm. 2017 Sep;14(9):1297-1301.

LAA morphology and stroke





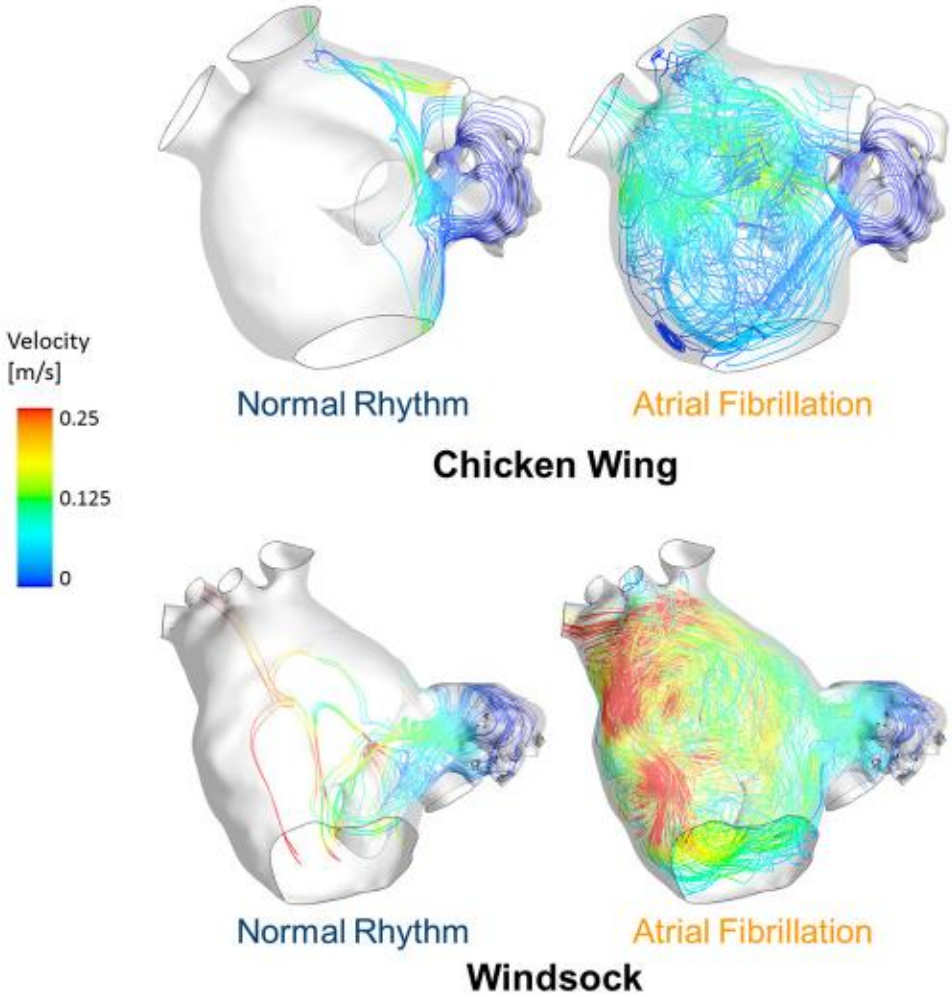
Non-Chicken wing morphology was associated with
Higher Hx of stroke/TIA



932 pts with AF
CT or MRI before RFCA
Retrospective, cross sectional design (odds ratio)
Anticoagulation status – unknown
LAA velocity and size were not associated to stroke, in this data.

L. Di Biase, et al. J Am Coll Cardiol 2012:60;531-8

LAA morphology may associated with LAA flow: Computational flow dynamics of LA

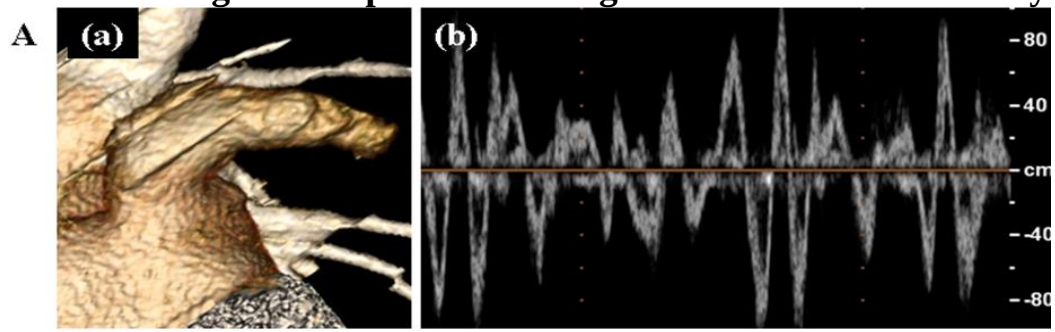


"Lowest washout of contrast agent was observed for the Cauliflower morphology"

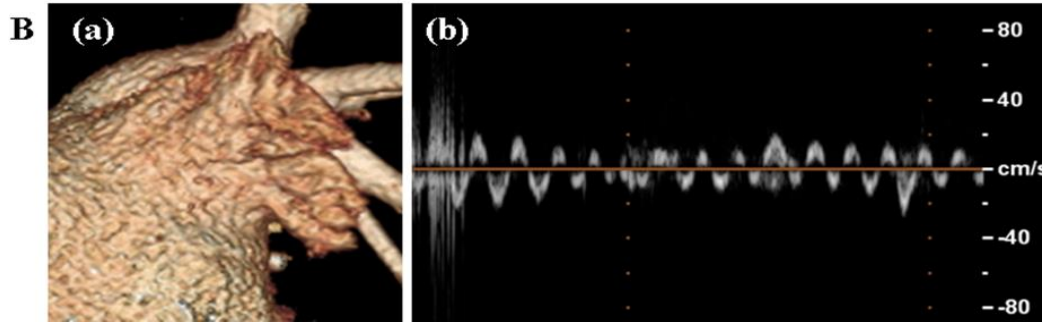
(2018) Computational Fluid Dynamic Analysis of the Left Atrial Appendage to Predict Thrombosis Risk. Front. Cardiovasc. Med. 5:34.

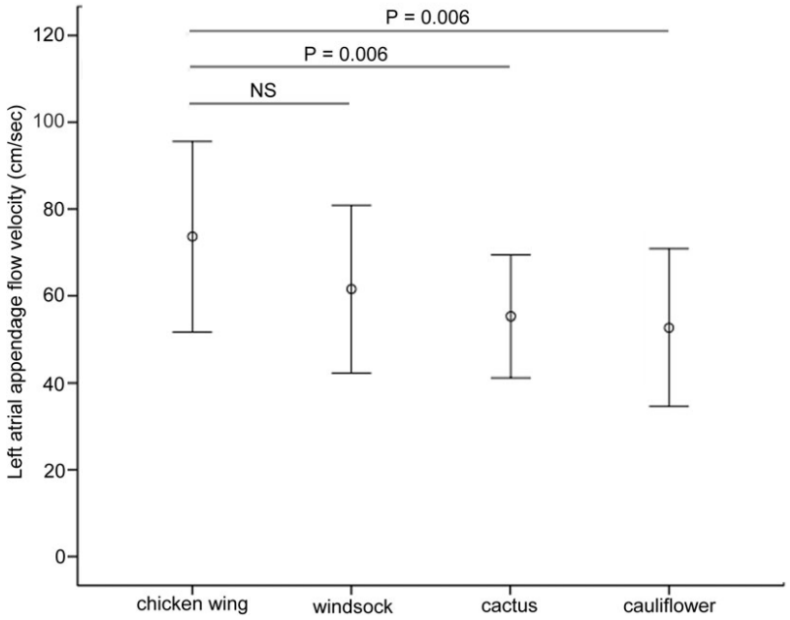
LAA morphology is associated to LAA flow velocity by TEE.

Chicken Wing LAA of patient showing normal LAA flow velocity.



Cauliflower type LAA with decreased LAA flow velocity

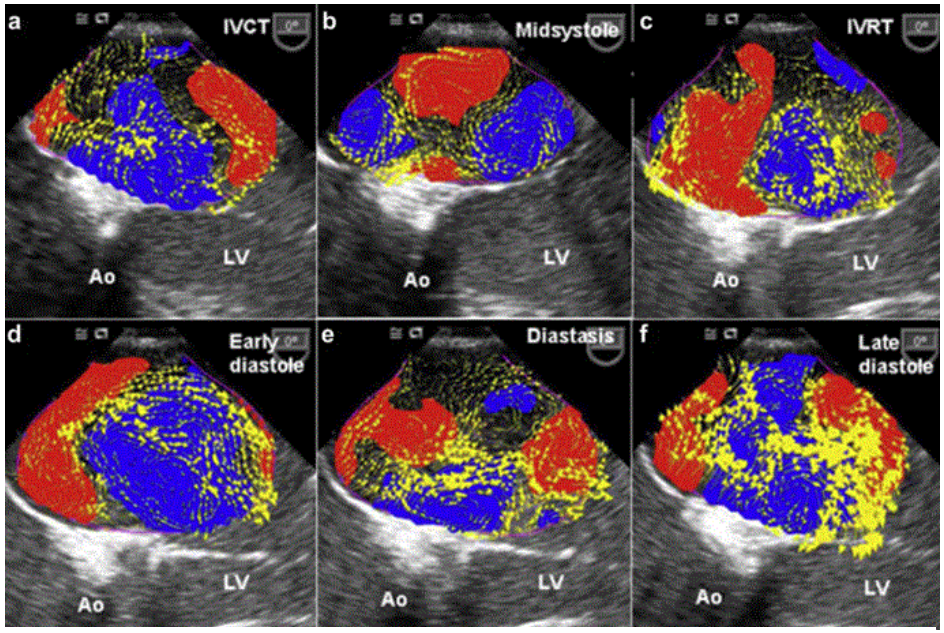




Lee JM, Seo J et al. J Cardiovasc Electrophysiol, 2015:26;922-927
H Kishima, et al. Circ J 2015;79:1706-1711
K Fukushima, et al. European Heart Journal-Cardiovascular Imaging 2016:17;59-66

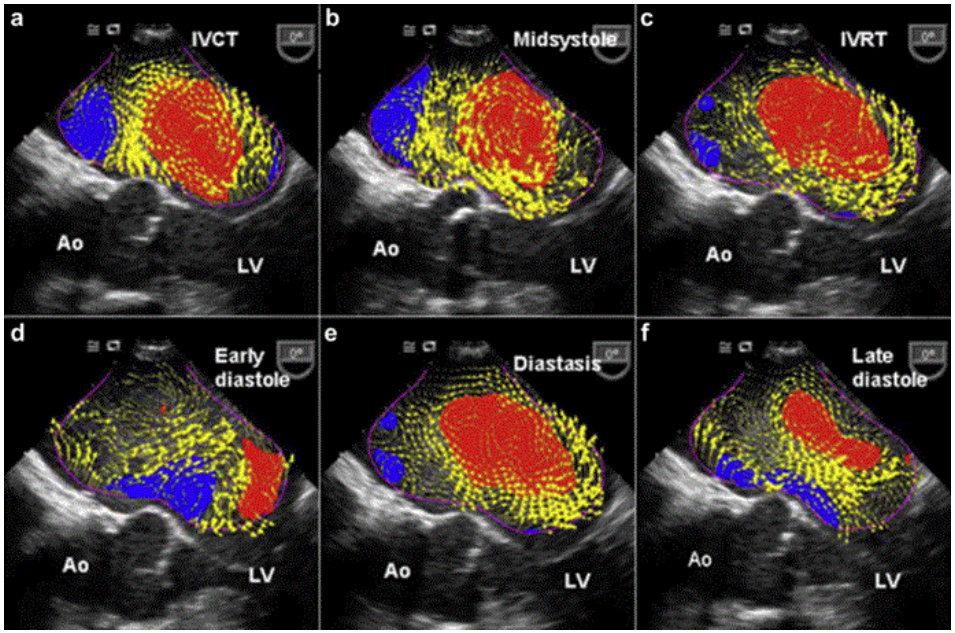
Particle image velocimetry: Comparison of LA vortex between SR and AF

SR



Multiple, pulsatile, compact and elliptical-shaped vortices were seen in the periphery of the LA.
These vortices were persistently maintained and vectors were directed toward the atrioventricular inflow.

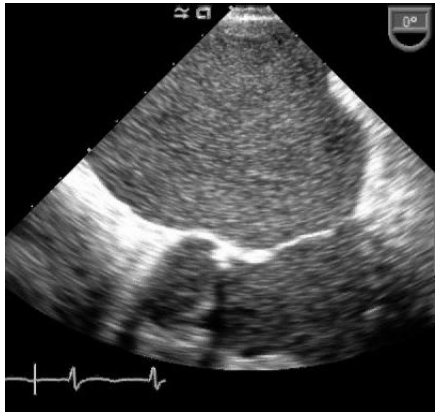
AF



A large, merged, lower pulsatile and round-shaped vortex was observed in the center of the LA.

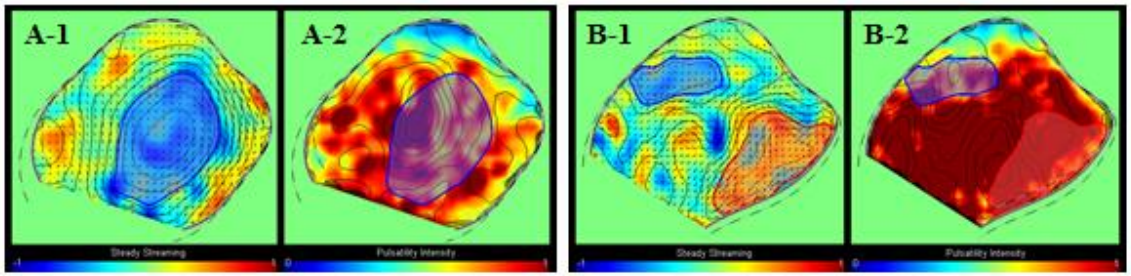
KH Park, GR Hong et al. Ultrasound Med Biol 2013

Particle image velocimetry by TEE



Patient A
M/46, PeAF, LAVI 44 ml/m^2
CHADS$_2$=1, LAAV 45 cm/s

Patient B
M/63, PeAF, LAVI 48 ml/m^2
CHADS$_2$=1, LAAV 45 cm/s



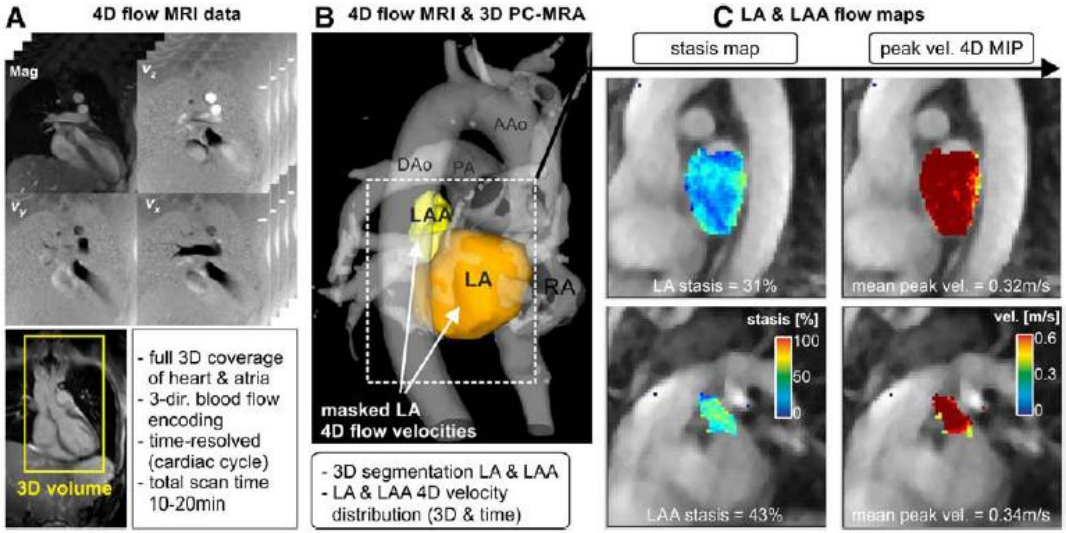
RS=1.41
LA voltage=0.41 mV
ERAF(+)

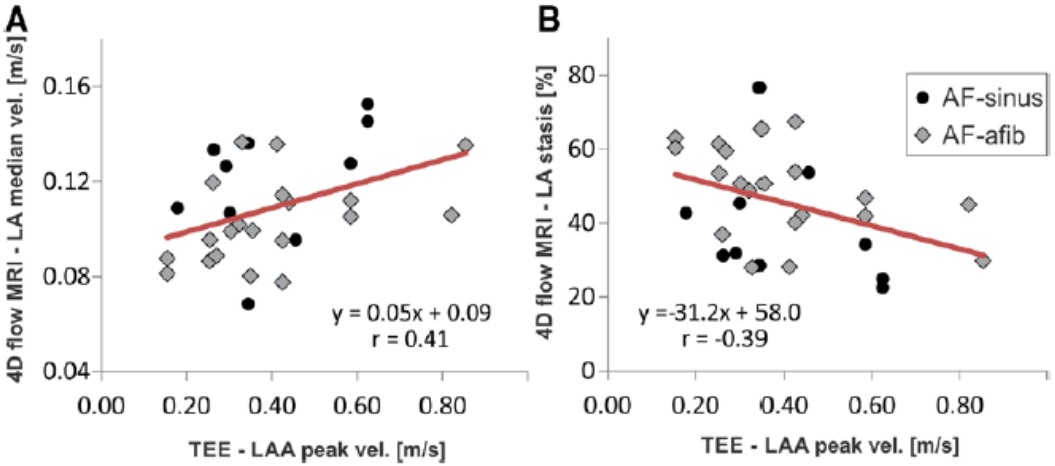
RS=2.32
LA voltage 1.74 mV
ERAF(-)

- **More ERAF in lower pulsatility (RS: relative strength) group**
- **Impaired LA flow might be associated with electrical remodeling and recurrent AF**

JM Lee, GR Hong, HN Pak et al. IJC imaging 2015;31:1139-1148

LAA flow by MRI

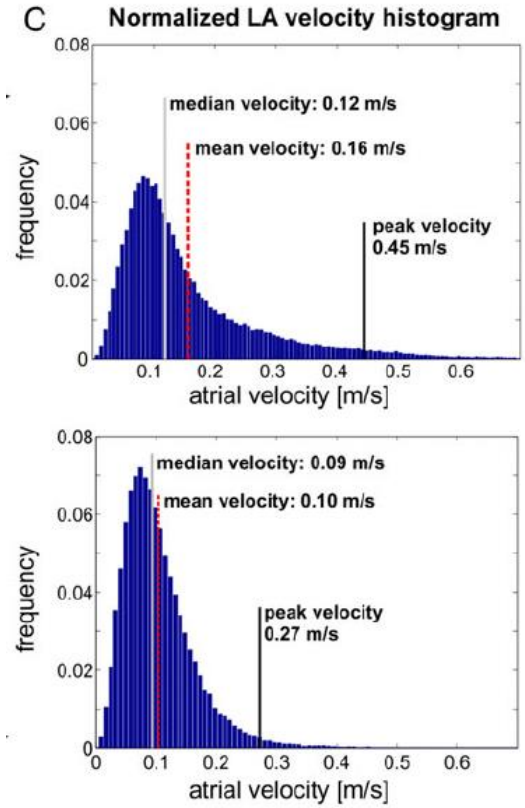




MRI-measured LAA flow velocity

Correlated with TEE-measured velocity

Flow velocity was lower in AF than NSR



M Markl et al.

Circ Cardiovasc Imaging. 2016 Sep;9(9):e004984

EHJ – Cardiovascular Imaging (2016) 17, 1259–1268

Summary

- **ESVEA on Holter, AHRE on CIED, SAECG P wave duration can predict AF and stroke.**
- **Increased LA volume, increased LA fibrosis, and impaired LA function are the main hallmarks of LA remodeling, and showed increased risk of stroke**
- **LAA is particularly associated with risk of stroke.**
- **Decreased LAA flow, enlarged LAA, some morphologic characteristics of LAA can predict stroke risk**
- **Intracardiac flow studies are emerging, but need more data for clinical application.**

Thank you for attention