Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation?: results from a multicenter study.

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Does the left atrial appendage morphology correlate with the risk of stroke in patients with Atrial Fibrillation? Result from a multicenter study.

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Abstract

Background: The left atrial appendage (LAA) represents one of the major sources of cardiac thrombus formation responsible for TIA/stroke in patients with atrial fibrillation(AF).

Objective: We studied LAA by computed tomography (CT) and by magnetic resonance (MRI) to categorize different morphologies and to correlate the morphology with the history of stroke/ transient ischemic attack (TIA).

Methods: The study population consisted of 932 patients with drug refractory AF planning to undergo transcatheter ablation. All patients underwent cardiac CT or MRI and care was taken to obtain LAA frames. All patients were screened for history of TIA/stroke. LAAs were categorized into different morphologies which included Cactus, Chicken Wing, Windsock, and Cauliflower.

Results: CT images of 499 patients and MRI images of 433 patients were analyzed (59±10 yrs, 79% male, BMI 27±4, EF 60±7, 14% $CHADS_2 \geq 2$). The distribution of different LAA morphologies was: Cactus [278 (30%)], Chicken Wing [451 (48%)], Windsock [179 (19%)], and Cauliflower [24 (3%)]. Out of the 932 patients, 73 (8%) patients had prior history of ischemic stroke or TIA. The prevalence of pre-procedure stroke/TIA in Cactus, Chicken Wing, Windsock, and Cauliflower morphologies were 12%, 4%, 10%, and 18% respectively ($p = 0.003$). After controlling for $CHADS_2$ score, gender, and AF types in a multivariable logistic model, Chicken Wing morphology was found to be 79% less likely to have a stroke/TIA history (OR 0.21, 95% CI 0.05-0.91, p=0.036). In separate multivariate model we entered chicken wing as reference group and assessed the likelihood of stroke in other groups in relation to reference. Compared to chicken wing, Cactus had 4.08 times (p= 0.046), Windsock- 4.5 times (p=0.038), and Cauliflower 8.0 times (p=0.056) more likely to have suffered a cerebrovascular ischemic event. The same results were confirmed in the subgroup of patients at low thromboembolic risk.

Conclusion: This study suggests that patients with chicken wing LAA morphology are less likely to have an embolic event even after controlling for potential confounders. If confirmed, these results could have a relevant impact on the anticoagulation management of patients with a low-intermediate risk for stroke/TIA.

Introduction

The left atrial appendage (LAA) represents one of the major sources of cardiac thrombus formation responsible for TIA/stroke in patients with atrial fibrillation (AF) (1,2). Its anatomical structure is challenging (3). Embriologically it is a remnant of the primordial left atrium. It lies anteriorly in the atrioventricular sulcus in close proximity to the left circumflex artery, the left phrenic nerve and the left pulmonary veins (3,4,5).

The shape of the LAA is variable. Several studies have described the LAA as a long tubular and hooked structure with different lobes. The imaging of the different structures and lobes is of utmost importance to diagnose the presence of LAA thrombus especially in patients with non-valvular AF (3,6,7,8).

The widespread utilization of left atrium ablation procedures and the presence of LAA occlusion devices for the treatment of patients with AF has increased the interest for this structure (9,10,11). Multidetector computerized tomography (CT) and magnetic resonance imaging (MRI), are well known imaging techniques able to detect high quality images of the LAA (12,13).

We quantitatively studied various morphologic parameters of the left atrial appendage (LAA) by computed tomography (CT) and by magnetic resonance (MRI) to categorize different LAA morphologies, and tried to correlate the different morphologies with the patient history of stroke/TIA.

Methods

Patient population

The study population consisted of 932 patients with drug refractory AF planning to undergo transcatheter ablation. All patients underwent cardiac CT or MRI and care was taken to obtain LAA frames. All patients were screened for previous history of TIA/stroke. $CHADS_2$ score was obtained in all patients. LAAs were categorized into different morphologies by CT scan and MRI which included Cactus, Chicken Wing, Windsock, and Cauliflower (see below and Table 1).

Echocardiograhy TT/TE parameters

CT

Cardiac CT imaging of the LAA was performed as previously described (3). Briefly, patients were scanned with contrast-enhanced ECG gated CT scan (Lightspeed Ultra, GE Healthcare, VA, USA). The slice acquisition thickness ranged from 0.625 to 1.25 mm. Three-dimension structures of the left atrium and LAA, were constructed using the volume rendered postprocessing technique. Standard measurements of LAA volume, velocity, and diameters were obtained. The morphology of the LAA was also evaluated using multiplanar reconstruction. LAA morphologies were classified by two expert cardiac CT radiologists, who were blinded to the clinical data and history of previous stroke/TIA.

MRI

Contrast-enhanced magnetic resonance imaging of the left atrium was performed by intravenous administration of 0.2 mmol/Kg of contrast agent (Gadobutrolo, GADOVIST®, Bayer S.P.A., Berlin, Germany), followed by a bolus of 20 mL of physiological solution. Images were obtained with a body-array coil 1.5 Tesla magnetic resonance imaging system (Magneton Avanto® 1.5T, Siemens, Erlangen, Germany). Three dimensional (3D) magnetic resonance angiography (MRA) was obtained with a breath-hold 3D fast-field Spoiled Gradient Echo (SPGR) imaging sequence performed in sagittal, coronal and axial views to obtain an anatomical view of the entire thorax. A narrow bandwidth of 31.25 kHz was used to reduce noise and improve the signal-to-noise ratio. The fractional echos (echo time of 1.08 ms) were used to provide $T1$-weighting and minimize flow artifacts and a flip angle of 20° was chosen to enhance background suppression. The final 3D volume was acquired as a coronal slab (typical field-of-view 40 cm, range 36-44 cm), using a rectangular field-of-view to decrease the acquisition time of the sequence. The bolus tracking technique (CARE-bolus) guaranteed the highest left atrium signal intensity by starting a multiphase SPGR image series in a coronal view at the exact time during which the bolus passed through the left ventricle-aortic root.

In order to keep speed magnetization in steady-state during the acquisition (repetition time 2.84 ms), contrast-enhanced MRA measurements were not ECG-gated. Another reason not to use gating was that entire measurement time had to be minimized to follow the bolus of the contrast agent. Motion artifacts from breathing were eliminated by patient's breath-hold for the time of the sequence (below 15 sec). Standard measurements of LAA volume and diameters were obtained following volume rendering and integration in the Polaris image processing package of the Carto-Merge system (Biosense Webster, Diamond. Bar, California, USA). LAA morphologies were determined by two expert cardiac MRI radiologists, who were blinded to the clinical data and history of previous stroke/TIA.

Classification of LAA Morphology

Based on its morphologies, the LAA was classified as:

(1) The Cactus LAA, with a dominant central lobe with secondary lobes extending from the central lobe in both superior and inferior directions (Figure 1).

(2) The Chicken Wing LAA, with an obvious bend in the proximal or middle part of the dominant lobe, or folding back of the LAA anatomy on itself at some distance from the perceived LAA ostium. This type of LAA may have secondary lobes or twigs (Figure 2).

(3) The WindSock LAA, with 1 dominant lobe of sufficient length as the primary structure. Variations of this LAA type arise with the location and number of secondary or even tertiary lobes arising from the dominant lobe (Figure 3).

(4) The Cauliflower LAA, with limited overall length with more complex internal characteristics. Variations of this LAA type have a more irregular shape of the LAA ostium (oval vs. round), a variable number of lobes with lack of a dominant lobe (Figure 4).

Statistical analysis

All continuous data are presented as mean ± standard deviation and were compared using analysis of variance (ANOVA) or Kruskal-Wallis test where appropriate. Categorical variables are described as count and percent and compared by using Pearson's chi-square or Fisher's exact test. Since classification into different LAA categories was determined by different operators using CT and MRI, we tested inter-operator concordance. Cohen's Kappa was utilized to assess estimate inter-rater agreement. Multivariable logistic model was used for identifying significant predictors of stroke/TIA. All potential confounders were entered into the model based on known clinical relevance, or significant association observed in univariate analysis. The controlling variables used in the model were- age, gender, hypertension, diabetes, AF types, and $CHADS_2$ score. Based on the components of the CHADS2 score, except the history of previous stroke/TIA, the study population was stratified into two sub-groups with low and intermediate/high risk of thromboembolisms (CHAD 0-1 and ≥2) and a sub-analysis was performed to investigate the possible association of LAA types with stroke/TIA within each group. The odds ratio (OR) and 95% confidence interval (CI) of stroke/TIA were computed. All tests were two-sided and a P-value <0.05 was considered statistically significant. Analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

CT images of 499 patients and MRI images of 433 patients (59±10 yrs, 79% male, BMI 27±4 Kg/m^2, EF 60±7%, 14% $CHADS_2$ ≥2) presenting for catheter ablation of AF were prospectively collected. The distribution of LAA morphologies was: Cactus [278 (30%)], Chicken Wing [451 (48%)], Windsock [179 (19%)] and Cauliflower [24 (3%)]. No statistically significant bias was noted in classifying LAA morphology by operators using CT and MRI (Kappa = 0.67; 95% CI 0.48-0.87, p = 0.001).

Table 1 presents the baseline demographic, clinical characteristics, and LAA measurements for the 4 LAA types. No differences were found in the incidence of congestive heart failure, hypertension, diabetes, dyslipidemia, or coronary artery disease. The groups were different with respect to gender, history of stroke/TIA, and $CHADS_2$ score of ≥2. The windsock type was more likely to be male. In addition, compared to other groups, Chicken Wing was the most prevalent LAA morphology (48%), had the lowest prevalence of prior stroke/TIA (4%), and $CHADS_2$ ≥2 (9%). No difference was noted for left atrium diameter, left ventricular ejection fraction (LVEF).

<u>Prevalence of pre-procedure stroke/TIA:</u>

In the study cohort, 78 (8%) of the 932 patients had a history of stroke/TIA prior to AF ablation. The distribution of the event (stroke/TIA) was significantly different across the LAA types [Cactus, Chicken Wing, Windsock, and Cauliflower were 35 (12%), 20 (4%), 19 (10%), and 4 (18%) respectively ($p < 0.001$)].

Table 2 compares the clinical characteristics of patients with and without stroke/TIA history. The Cactus type was significantly more likely to have had a stroke (44% with-stroke had cactus type whereas 28% of stroke-free had cactus morphology, $p = 0.002$). On the other hand, Chicken Wing was strongly associated with absence of history of stroke ($p < 0.001$). As expected, a difference in $CHADS_2$ scores was found to be significant between stroke and no history of stroke (table 2).

<u>Univariable Analysis</u>

As revealed from univariable analysis, patients with history of stroke/TIA were more likely to have cactus type LAA [odds ratio (OR) 2.5, 95% CI 1.02 to 6.08, p=0.045], and $CHADS_2$ score ≥2 (OR 24, 95% CI 9.93 to 60.8, p<0.001), and those with Chicken Wing morphology were significantly less likely to have had stroke/TIA (OR 0.18, 95% CI 0.04 to 0.77, p= 0.021). The OR and 95% CI for baseline risk factors are shown in table 3.

Multivariable Analysis

After controlling for $CHADS_2$ score, gender, and AF types in a multivariable logistic model, Chicken Wing was found to be 79% less likely to have a stroke/TIA history (OR 0.21, 95% CI 0.05-0.91, p=0.036). In separate multivariate model we entered Chicken Wing as reference group and assessed the likelihood of stroke/TIA in other groups in relation to reference. Compared to Chicken Wing, Cactus had 4 times (OR 4.08, 95% CI 1.04 to 17.27, p= 0.046), Windsock 5 times (OR 4.8, 95% CI 1.89 to 22.50, p=0.038), and Cauliflower 8 times (OR 8.02, 95% CI 0.92 to 27.86, p=0.056) more likely to have a stroke/TIA history. Overall, the odds ratio for stroke/TIA in non-Chicken Wing LAA morphology was 2.95 (95% CI 1.75-4.99, p=0.041) compared to Chicken Wing.

LAA morphology and risk of stroke/TIA in low-risk patients

Also among patients with CHAD 0-1, Chicken Wing LAA had the lowest risk of previous stroke/TIA. Indeed, stroke was significantly more prevalent in non-Chicken Wing morphology compared to the Chicken Wing category (4.6% vs. 0.7%, p=0.001). After adjusting for gender, AF type, and LA size, Chicken Wing morphology was found to be an independent predictor of stroke (OR 10.1, 95% CI 1.25 to 79.7, p=0.019).

Discussion

This is the first paper correlating different LAA morphologies as obtained with CT and or MRI images with the presence of TIA/stroke.

We found that patients with the Chicken Wing LAA morphology have a statistically significant lower risk of previous stroke/TIA when compared to all the remaining LAA morphology described. The Chicken Wing LAA morphology was the most prevalent one (48% of our population), and the least associated with history of stroke/TIA.

These results are novel and could be clinically relevant, especially for patients currently judged at low risk of thromboembolic events, such as those with CHAD scores of 0 and 1. In these patients, the presence of a non-Chicken Wing LAA morphology strikingly increases the risk of thromboembolic events (up to 4.6%, corresponding to a 10-fold increased risk of stroke/TIA), which suggest the appropriateness of a more aggressive antithrombotic therapy.

Further, this study may provide insights into why stroke/TIA has been described also in patients with a theoretical low risk of thromboembolsims (CHAD score of zero).

The physician and the technician acquiring the CT and the MRI images were blinded to the patient's history, which minimize the risk of bias; in addition, all the statistical analyses were corrected for all possible confounders, and demonstrated no interaction between the $CHADS_2$ score and the risk of stroke/TIA linked to different LAA morphologies.

Anatomical and Mechanical Concepts

The LAA is an embryological remnant that functions during conditions of fluid overload as reservoir (6). Due to its hooked morphology, the LAA is prone to stasis and for this reason, represents the prevalent site of thrombus formation in patients with AF (6). Several variables have been described to be associated with thrombus formation.

Leung et al and Manning et al. (1-7) with trans-esophageal evaluations reported that up to 98% of atrial thrombi occurring during AF derive from the LAA.

The LAA size is associated with increased thromboembolic risk (14). Autopsy studies have reported a direct association between the LAA size and the risk for stroke/TIA especially in patients with non valvular AF (15,16). In our study, no significant correlation between LAA size and the risk of stroke/TIA was found (Table 2).

To date, there is no data correlating the various LAA morphologies with the thromboembolic risk of stroke/TIA in patients with AF.

Anticoagulation Management

The $CHADS_2$ score was introduced into guidelines and implemented into clinical practice to assess individual thromboembolic risk in patients with AF. In patients with $CHADS_2$ score more than 1 the need for oral anticoagulation is not questionable, but in patients with low-intermediate risk for stroke ($CHADS_2$ score = 1) no consensus exist on whether patients should receive oral anticoagulation or antiplatelet therapy (17,18). Recently with the aim to reduce the risk for stroke in patients with AF and identifying a higher number of patients at risk, a new score has been proposed by the European guidelines: the CHA_2DS_2-VaSc score (19). Although with this new score a higher number of patients are required to use oral anticoagulation, the clinical decision making is still controversial in patients with low-risk CHA_2DS_2-VaSc score; the implementation of LAA morphology may aid the clinical decision toward oral anticoagulant or antiplatelet therapy. Importantly, it should not be forgotten that the risk for stroke should be balanced with the risk for bleeding, which is another dramatic complication is patients with AF treated with anticoagulants. In patients with contraindication to Warfarin or due to physician e/o patient's preference it is possible to use antiplatelet therapy although with contrasting results (17,18,19).

In this scenario the identification of an appendage morphology associated with a lower risk for stroke may further guide the clinicians in the decision process.

The present study suggests that the LAA morphology should be taken into account when planning the anticoagulation management of patient with AF. The LAA morphology remained the most powerful independent predictor of stroke/TIA also after adjustment for the $CHADS_2$ score at multivariable regression analysis, which further strengthens the relevance of our findings. Of note, LAA morphology was confirmed a powerful predictor of thromboembolic events also in the subgroup of patients with a low-intermediate baseline risk of stroke/TIA, such as those with $CHADS_2$ scores of 0 to 1.

The advent of the new oral anticoagulants with improved thromboembolic protection, lower risk of bleeding, and better patient compliance, may justify the appropriateness of early antithrombotic therapy in patients at lower risk of thromboembolic events and non-Chicken Wing LAA morphology (20,21,22). The cost-effectiveness of such anticoagulation management when compared to warfarin will need further investigation.

Study Limitation

Although retrospective, this study included a large sample size. We could not be able to retrieve drug treatment, and specifically the antiaggregation/anticoagulation status at the time of the event, which may potentially affect the results in patients at high risk of stroke (i.e., $CHADS_2$ scores ≥ 2). Although this might be considered a major limitation, the strong independent statistical association between LAA morphology and risk of stroke is of utmost clinical relevance.

Conclusion

This study suggests that patients with non-Chicken Wing LAA morphology are significantly more likely to have an embolic event, even after controlling for potential confounders. If confirmed, these results could have a relevant impact on the anticoagulation management of patients with AF, especially of those with an intermediate-low risk for stroke (i.e., $CHADS_2$ score 0 to 1) in whom oral anticoagulant therapy is currently not recommended.

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Table 1: Baseline Characteristics

	Overall Population	Type 1 (Cactus)	Type 2 (Chicken Wing)	Type 3 (Windsock)	Type 4 (Cauliflower)	P value	Groups with pair-wise significant difference
N=932	**932**	**278**	**451**	**179**	**24**		
Age, yrs	59±10	59±09	57±11	59±10	62±15	0.097	
Male	734(79%)	218(78%)	356(79%)	147(82%)	13(55%)	0.019	4 vs. 3; 4 vs. 2
AF Type							
PAF	548(59%)	167(60%)	266(59%)	100(56%)	15(64%)	0.810	
PER	336(36%)	89(32%)	167(37%)	73(41%)	7(28%)	0.235	
LSP	48(5%)	22(8%)	18(4%)	6(3%)	2(8%)	0.086	
AF Duration, months	59±65	67±77	30±41	50±62	47±46	0 .404	
BMI	27±04	27±04	27±04	27±03	26±03	0.906	
Dyslipidemia	218(23%)	68(25%)	99(22%)	47(27%)	4(18%)	0.565	
Hypertension	450(48%)	143(52%)	201(45%)	95(53%)	11(45%)	0.150	
CHF	42(5%)	9(3%)	19(4%)	13(7%)	1(4%)	0.212	
Diabetes	40(4%)	19(7%)	13(3%)	6(4%)	2(9%)	0.547	
Prior stroke/TIA	78(8%)	35(12%)	20(4%)	19(10%)	4(18%)	<0.001	2 vs. 1; 2 vs. 3
CAD	45(5%)	15(5%)	24(5%)	4(2%)	2(9%)	0.643	
CHADS2 0	428(46%)	115(42%)	237(53%)	67(37%)	8(33%)	<0.001	2 vs. 3; 2 vs. 1
CHADS2- 1	377(40%)	111(40%)	173(38%)	84(47%)	9(36%)	0.258	
CHADS2 ≥2	127(14%)	52(19%)	41(9%)	28(16%)	7(27%)	<0.001	2 vs. 1; 2 vs. 4
LV EF, %	60±07	60±08	59±07	60±07	60±02	0.895	
LAA volume	14.26±06.17	14.63±07.58	//	14.98±06.71	//	0.781	
LAA Velocity, mm	74.54±25.43	69.45±28.43	77.34±26.34	79.04±29.84	78.00±18.39	0.257	
LAA AP Diameter, mm	45.36±06.77	46.07±05.90	44.33±06.95	46.68±06.76	42.50±06.66	0.029	
LAA Longitudinal Diameter	60.70±07.83	62.07±08.05	58.49±07.99	61.55±07.94	56.50±07.92	0.067	
LAA Lat-Median Diameter	46.24±07.59	47.05±08.30	45.61±07.29	47.50±07.67	43.67±04.03	0.192	

Table 2: Baseline characteristics according to event (Stroke/TIA)

	No History of Stroke/TIA (n-854)	Prior Stroke/TIA (n=78)	P value
N=932	**854**	**78**	
Age, yrs	58±10	62±8	0.304
Male	674(79%)	60(76%)	0.679
LAA Type			
Cactus	243(28%)	35(44%)	0.002
Chicken Wing	431(50%)	20(26%)	<0.001
Windsock	160(19%)	19(24%)	0.228
Cauliflower	20(2%)	4(5%)	0.137
BMI	27±04	27±04	0.908
Dyslipidemia	193(23%)	25(32%)	0.059
Hypertension	409(48%)	41(53%)	0.429
CHF	39(5%)	3(4%)	0.769
Diabetes	35(4%)	5(6%)	0.335
CAD	43(5%)	2(3%)	0.330
CHADS2= 0-1	783(92%)	21(27%)	<0.001
CHADS2 ≥2	71 (8%)	57(73%)	<0.001
LV EF, %	58±08	60±07	0.140
LAA volume	14.13±06.04	15.04±07.10	0.372
LAA Velocity, mm	74.77±25.93	72.26±20.23	0.220
LAA AP Diameter, mm	45.36±06.76	45.40±06.90	0.822
LAA Longitudinal Diameter, mm	60.64±07.97	61.54±05.83	0.062
LAA Lat-Median Diameter, mm	46.27±07.49	45.81±08.81	0.216

Table 3: Univariate Odds Ratio for stroke/TIA.

Variable	Odds Ratio 95% CI	p value
Age, yrs	1.04(1.00-1.09)	0.045
Gender (Male)	1.17(0.51-2.68)	0.708
LAA Type		0.000
Cactus	2.50(1.02-6.08)	0.045
Chicken Wing	0.18(0.04-0.77)	0.021
Windsock	1.13(0.40-3.17)	0.821
Cauliflower	1.99(0.23-17.23)	0.534
CHADS2 ≥2	24.48(0.93-60.84)	<0.001
BMI	1.03(0.94-1.13)	0.562
Dyslipidemia	1.60(0.75-3.40)	0.225
Hypertension	1.23(0.61-2.47)	0.571
Diabetes	1.40(0.31-6.35)	0.659
LV EF, %	0.95(0.91-1.00)	0.050
ARB	1.17(0.46-2.93)	0.746
ACE Inhibitor	2.00(0.89-4.48)	0.094
Beta-blocker	0.72(0.33-1.59)	0.415
Aspirin/Plavix	0.30(0.07-1.28)	0.103
Lipid-lowering therapy	2.08(0.68-6.40)	0.200
LAA volume	1.02(0.94-1.11)	0.609
LAA Velocity, mm	1.00(0.98-1.02)	0.681
LAA AP Diameter, mm	1.00(0.95-1.06)	0.975
LAA Longitudinal Diameter	1.02(0.96-1.07)	0.571
LAA Lat-Median Diameter	0.99(0.94-1.05)	0.763

Figure legend

Figure 1: A CT scan and B MRI of a Cactus LAA morphology

Figure 2: A-B CT scan and C MRI of a Chicken Wing LAA morphology

Figure 3: A-B CT scan and C MRI of a Windsock LAA morphology

Figure 4: A CT scan and B MRI of a Cauliflower LAA morphology

Figure 5: Rate of stroke/TIA across Chicken Wing and non-Chicken Wing morphologies in patients with low thromboembolic risk (CHAD score 0-1). Non-Chicken Wing LAA morphology increases the risk of stroke/TIA more than 6-fold compared to Chicken Wing.

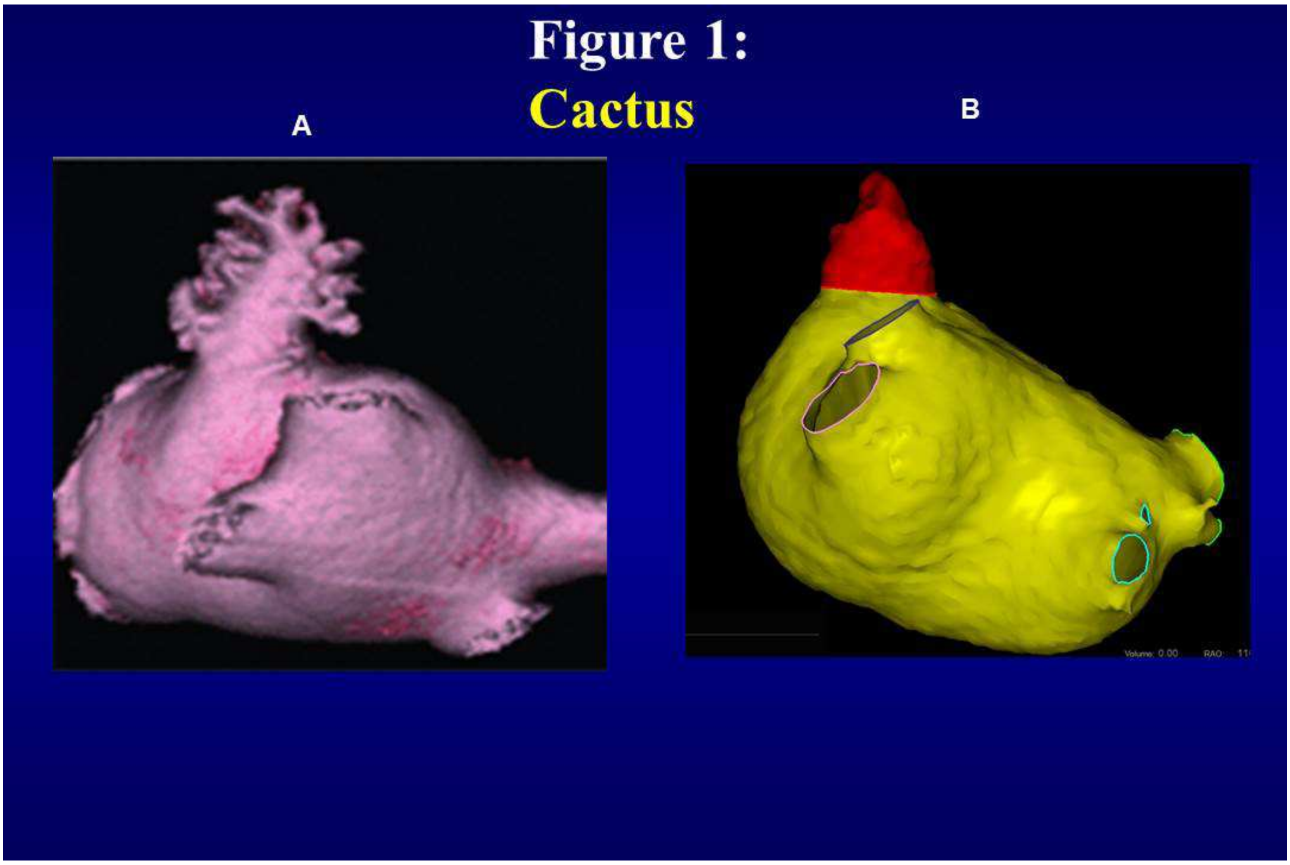
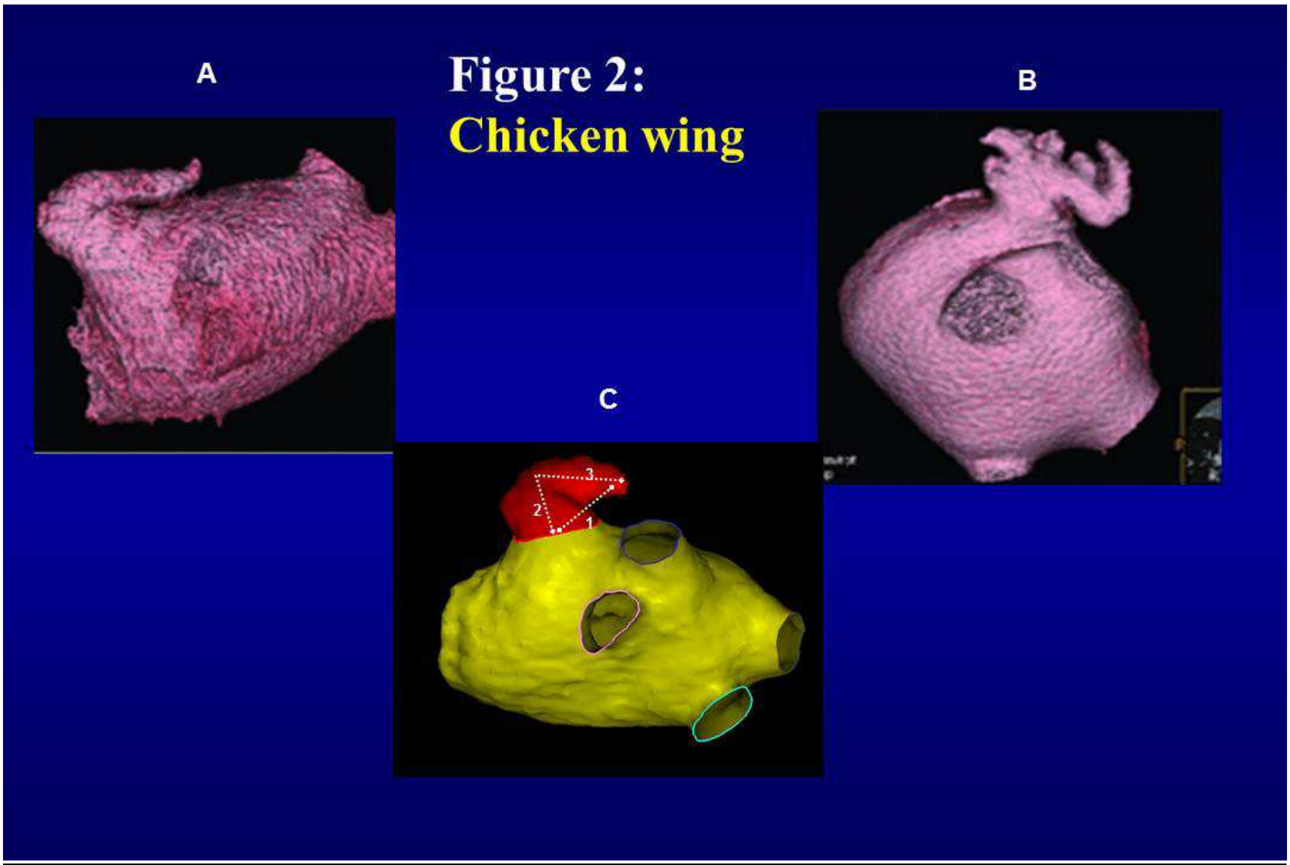
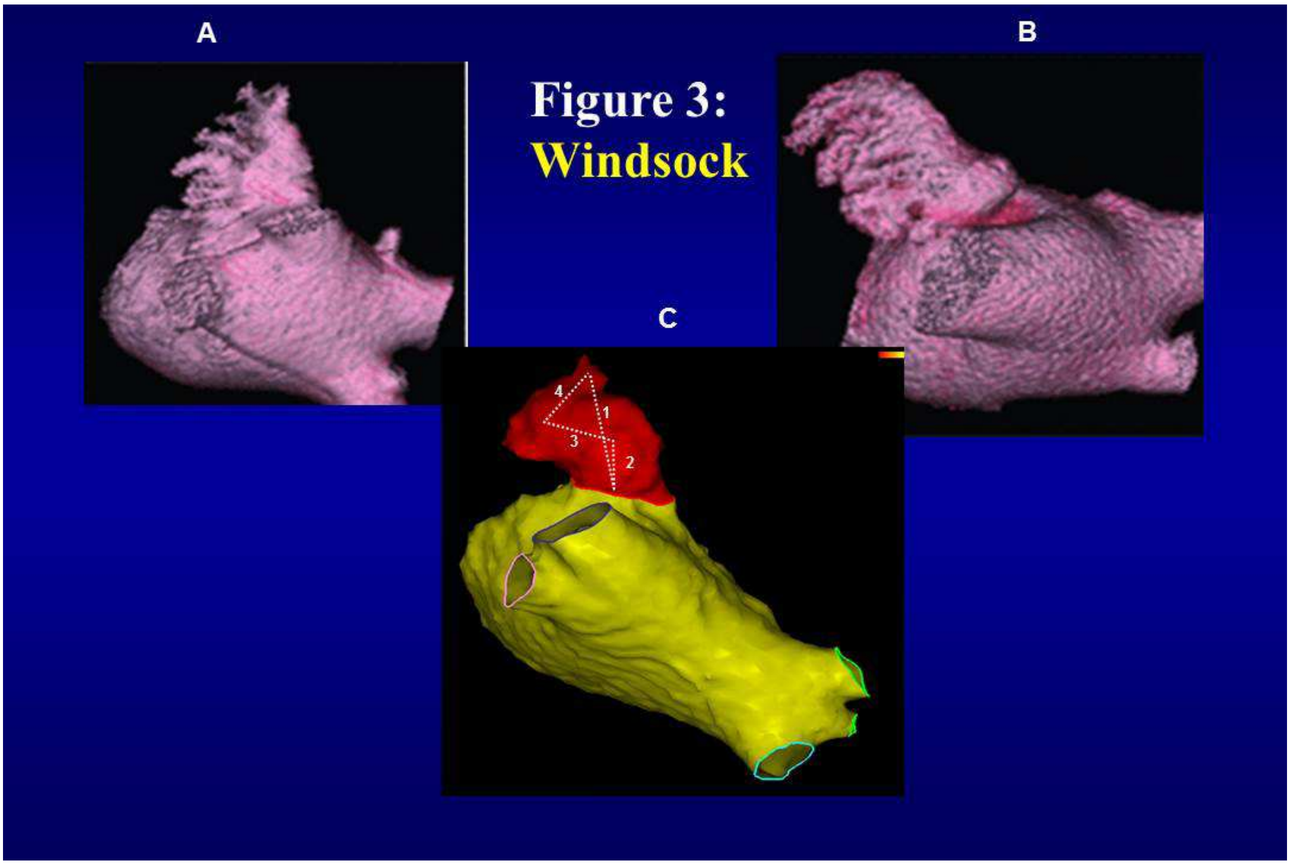


Figure 1:
Cactus
A
B


A
Figure 2:
Chicken wing
B
C
3
2
1


A
B
Figure 3:
Windsock
C
4
1
3
2

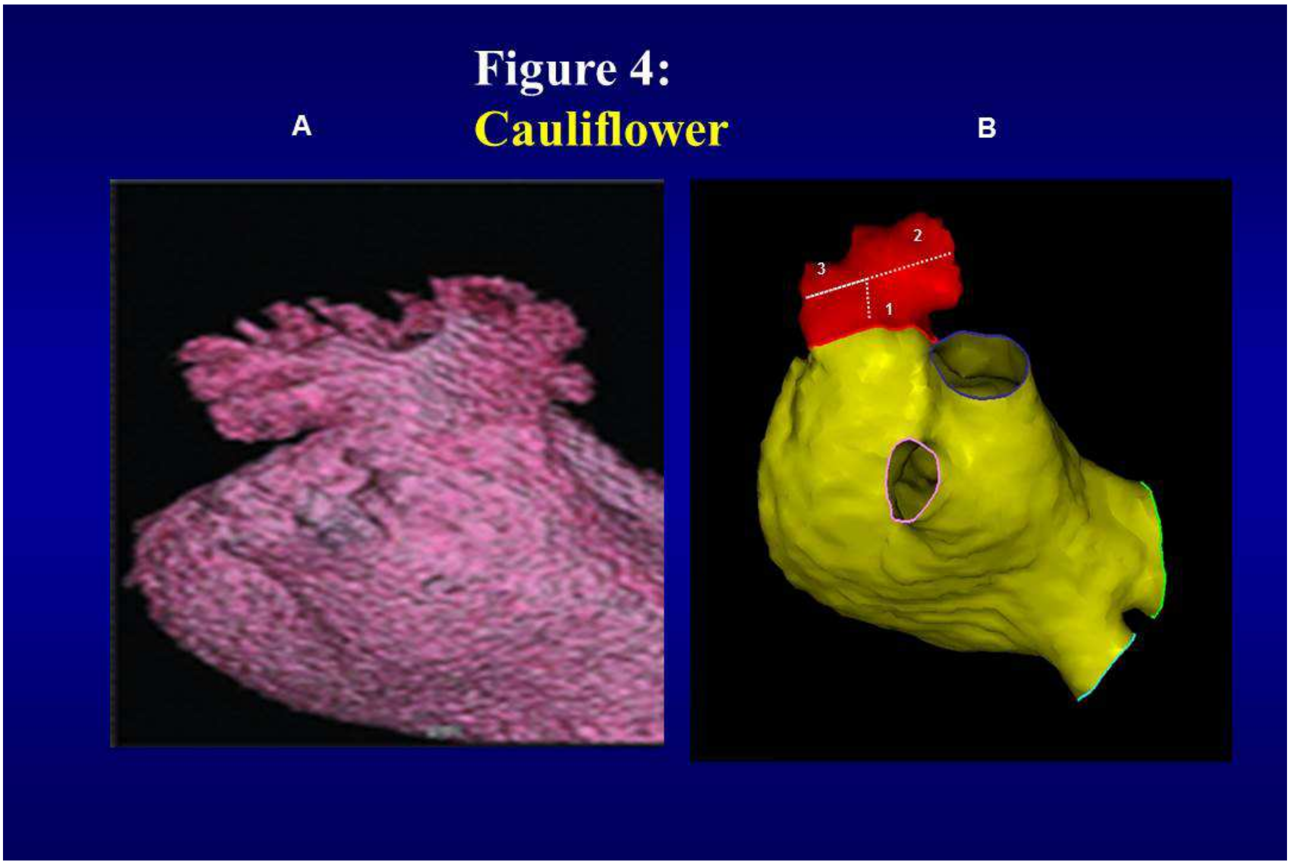


Figure 4:
Cauliflower
A
B
3
2
1

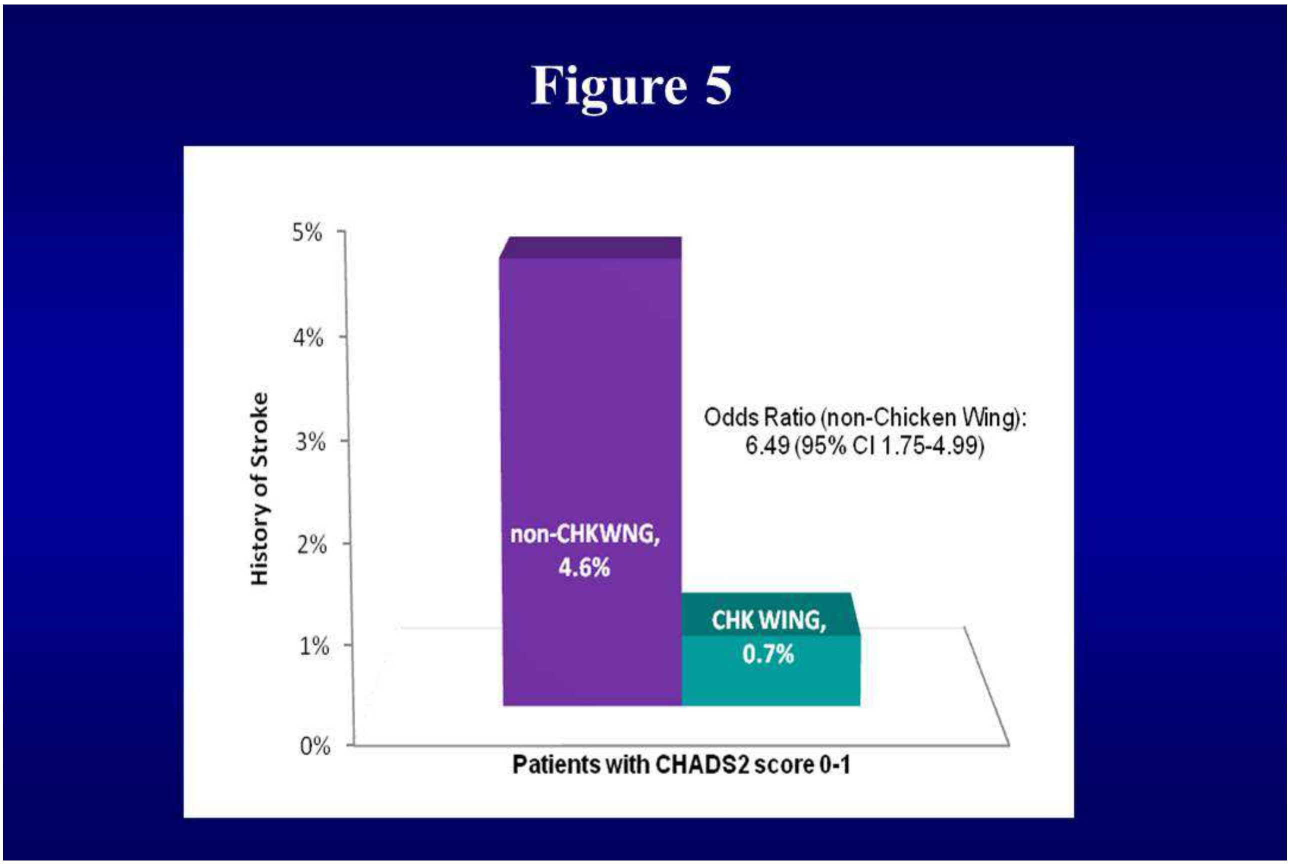


Figure 5
5%
4%
3%
2%
1%
0%
History of Stroke
non-CHKWNG,
4.6%
CHK WING,
0.7%
Odds Ratio (non-Chicken Wing):
6.49 (95% CI 1.75-4.99)
Patients with CHADS2 score 0-1