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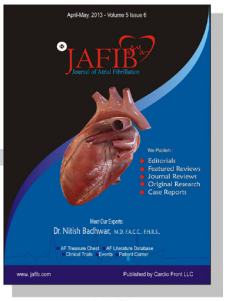

# The Prevalence of Low Left Atrial Appendage Emptying Velocity and Thrombus in Patients Undergoing Catheter Ablation for Atrial Fibrillation on Uninterrupted Peri-procedural Warfarin Therapy

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## Abstract

**Introduction: The 2012 HRS/EHRA/ECAS guidelines encourage pre-procedural transesophageal echocardiography (TEE) prior to ablation for atrial fibrillation (AF), but acknowledge a lack of consensus in patients maintained on therapeutic warfarin before, during and after the procedure. This is partly because the incidence of left atrial appendage (LAA) thrombus is so low, that it is hard to draw clear conclusion regarding the characteristics of patients who develop thrombus. We hypothesize that the presence of low LAA emptying velocities, which predisposes to thrombus, and/or thrombus itself can be predicted in patients undergoing ablation, based upon clinical characteristics and transthoracic echocardiography (TTE).**

**Methods: In this multicentre study, we undertook TTE and transesophageal echocardiograms (TEE) in 586 patients (age 59.9±0.4 years old, 64.5% male) undergoing catheter ablation for AF who were anticoagulated on warfarin (target international normalized ratio 2–3.5) for ≥3 consecutive weeks prior to procedure and maintained on warfarin for the procedure.**

**Results: Low peak LAA emptying velocities (<40cm/s) were identified in 111 (24.7%) patients and LAA thrombus was identified in 3 patients (0.5%) despite having therapeutic INRs. The 3 patients with thrombus had LAA emptying velocities of 23, 29 and 31 cm/s. None of the remaining patients had a peri-procedural stroke. Patients with peak LAA emptying velocities <40cm/s or thrombus on TEE had significantly ($p<0.05$) higher $CHA_2DS_2$-VASc scores (1.7± 0.1 v's 1.4±0.1), and were more likely to have impaired LVSF (odds ratio [95% CI]: 2.66 [1.52-4.66]), a LA diameter >4.6cm on TTE (2.40 [2.13-5.41]), or persistent AF (2.60 [1.63-4.14]) compared to those with a higher LAA velocity without thrombus.**

**Conclusion: In patients on uninterrupted warfarin therapy, a $CHA_2DS_2$-VASc score ≥1 or LA diameter >4.6cm on TTE identifies 91.5% of those at risk of developing thrombus with LAA emptying velocity of <40 cm/s and 100% of those with thrombus in our cohort.**

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## Introduction

Left atrial catheter ablation is considered by some to be a first line treatment for those with symptomatic paroxysmal atrial fibrillation (AF) and structurally normal hearts and as a second line therapy after anti-arrhythmic drugs for those with paroxysmal or persistent AF and structural heart disease.[1] The procedure carries a risk of thromboembolic stroke due to mobilisation of left atrial appendage (LAA) thrombus secondary to catheter manipulation or restoration of sinus rhythm. In order to minimize this risk, the 2012 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society statement [2] encourages pre-procedural transesophageal echocardiography (TEE) to screen for the presence of thrombus in patients at the time of the procedure. However it also acknowledges that there is a lack of consensus or data in patients that have been maintained on therapeutic oral anticoagulation. This is partly due to the fact that the incidence of LAA thrombus is so low, that it is hard to draw clear conclusion regarding the characteristics of patients who develop LAA thrombus. TEE is costly, time consuming and increases risk to the patient, therefore targeting TEE to those patients most likely to benefit is of importance.

A low peak LAA emptying velocity is a strong predictor of thrombus formation independent of rhythm. [3] A velocity of greater than 40cm/s correlates with successful cardioversion [4] and maintenance of sinus rhythm thereafter,[5] whilst a velocity of less than 40 cm/s [6, 7, 8, 9] best predicts thromboembolic risk. We hypothesized that the presence or absence of a low LAA emptying velocity and/or thrombus could be predicted in patients undergoing ablation, based upon clinical characteristics and transthoracic echocardiography (TTE) findings in a low-intermediate risk group maintained on warfarin therapy before, during and after the procedure.

## Methods

### Patients

We retrospectively evaluated the records of all patients put forward for left atrial ablation for symptomatic, drug refractory atrial fibrillation between March 2009 and March 2011 at the John Radcliffe Hospital, Oxford, and between January and December 2010 at St Bartholomew's Hospital, London, UK. Written informed consent was obtained from all patients prior to procedures. Procedures were classified as being for paroxysmal, or persistent AF, as well as a "re-do" procedure if a previous left atrial ablation had been performed. We documented patient age and sex, the presence of heart failure, hypertension, diabetes mellitus, prior stroke or transient ischemic attack (TIA), and vascular disease (prior myocardial infarction, peripheral artery disease, or complex aortic plaque), in order to calculate a $CHADS_2$ and $CHA_2DS_2$-VASc score. We also documented the left ventricular ejection fraction and LA diameter on transthoracic echocardiography, and peak left atrial appendage (LAA) emptying velocity and presence or absence of left atrial or left atrial appendage thrombus on TEE.

### Anticoagulation Protocol

For patients already taking warfarin, this was continued up to and including the ablation whereas those not previously on warfarin were commenced on treatment up to 6 weeks prior to the ablation aiming for at least 3 weeks in the therapeutic range of an International Normalized Ratio (INR) of 2 to 3.5 on weekly INR monitoring. INR was also checked again within 24 hours of the procedure in 577 patients, and 448 (77.6%) of patients had an INR of 2.0 or more at this point. Patients with a sub-therapeutic INR at this stage were given a once daily treatment dose of low molecular weight heparin from the morning following the procedure until the INR became therapeutic. Therapeutic warfarin was continued for at least 3 months after the procedure.

### Transthoracic and Transesophageal Echocardiography studies

All patients had a standard two-dimensional TTE by an experienced echocardiographer (TTE, Sonos 7500 and IE33, Philips, and Vivid 7, GE Healthcare) as part of their cardiological work up prior to ablation. Reports were reviewed retrospectively to obtain data on left atrial anteroposterior diameter (determined with M-mode scans from the parasternal long-axis view ensuring perpendicular cursor placement as guided by 2D echo, n=526) and degree of left ventricular impairment (classified as

normal, mild, moderate or severely impaired according to international guidelines (10), n=577). All patients also underwent TEE (IE33, Philips, or Vivid I, GE Healthcare) within the 24 hours prior to the planned ablation procedure by an experienced Consultant Cardiologist trained in TEE. Multiple planes of the LAA, including a continuous sweep from 0 to 180 degrees with short- and long-axis, were obtained from the mid-esophageal view. Reports were reviewed retrospectively to obtain data on the presence of LAA thrombus (defined as a circumscribed and uniformly echo-dense intra-cavity mass distinct from the underlying endocardium and pectinate muscles, present in more than 1 imaging plane) and peak LAA emptying velocity (measured via pulse wave Doppler positioned 1cm into the orifice of the appendage (11), n=450). If a thrombus was suspected, all images were reviewed by a second experienced Consultant Cardiologist trained in TEE, the ablation procedure was not performed and a repeat TEE was carried out after a further period of anticoagulation at a higher INR (3-4) to demonstrate resolution of the thrombus.

### Left Atrial Ablation

Ablation was performed under general anaesthesia or conscious sedation. Catheters were introduced percutaneously through the femoral veins and a transseptal puncture performed to access the left atrium. After transseptal access, a bolus of heparin was administered (according to patient weight) and further heparin administered to achieve and maintain an activated clotting time of 350 seconds. A three dimensional map was often constructed using an electroanatomical mapping system (CARTO (Biosense Webster), or NavX Velocity (St Jude Medical)) to assist in the location of catheters and position of ablation lesions. A 7 French circular mapping catheter with a deflectable loop was placed at the ostium of each pulmonary vein for mapping. Radiofrequency ablation was delivered through a 4mm irrigated-tip thermocouple-equipped catheter (using a target temperature of 48 degrees C at a power of 30-40W) with continuous lesions in a wide area circumferential fashion around ipsilateral pulmonary veins with an endpoint of bidirectional conduction block between the LA and pulmonary veins. Alternatively an Arctic Front cryoablation balloon catheter (Medtronic) was used to isolate each pulmonary vein individually. Where patients were in persistent AF, ablation of complex fractionated electrograms was also performed. Also for those patients in persistent AF or undertaking re-do procedures, lines of ablation lesions were deployed along the LA roof, and across the mitral isthmus. If sinus rhythm was not achieved by the end of the procedure, patients were cardioverted electrically.

### Follow-Up

All patients were followed up 3 months post procedure at which point, if rendered asymptomatic from AF, their warfarin was changed to aspirin in those with a $CHADS_2$ score of 0, to aspirin or warfarin for those with a $CHADS_2$ score of 1 (according to patient and clinician choice) and warfarin therapy continued in those with a $CHADS_2$ score of 2 or more. In those patients with continued symptomatic AF put forward for repeat procedures, patients remained on warfarin therapy.

### Statistical Analysis

Data are presented as mean ± standard error of the mean. Differences between groups were determined using an unpaired t-test and one-way ANOVA (with the post-hoc Tukey's test) for normally distributed data and the Mann-Whitney U and Kruskal-Wallis H tests (with the post-hoc Dunn's test) for non-parametric data. Pearson's coefficient (r) was used to correlate variables. Analysis of patient groups stratified by LAA emptying velocity was undertaken using univariate analysis; conducted with the Student's t-test, Mann Whitney U and Fisher exact test to compare continuous, categorical and dichotomous variables respectively. Multivariate analysis was undertaken using binary logistic regression. All statistical analysis was performed using SPSS (version 16.0) software with the exception of the Dunn's post-hoc test (GraphPad InStat version 3.06). Results were considered significant at $p<0.05$.

## Results

The clinical characteristics of 586 patients (357 from the John Radcliffe Hospital, Oxford, and 229 from St Bartholomew's Hospital, London, UK) are summarised in Table 1. The majority of patients (89%) had normal left ventricular systolic function and were low to intermediate risk (0/1) in terms of their $CHADS_2$ (84.8%) and $CHA_2DS_2$-VASc (53.1%)

scores.

TEE demonstrated a peak LAA emptying velocity less than 40 cm/s in 111 out of 450 patients (24.7%) and thrombus in 3 patients from 586 patients (0.5%). In all cases the thrombus was located in the LAA. This is despite all 3 having therapeutic INRs (2.2, 2.2 and 3.3 respectively). The 3 patients with thrombus did not go on to have their procedure but had a repeat TEE after 2-3 months of further treatment with warfarin at a higher INR (3-4), which confirmed resolution of thrombus in all cases. Of the patients without LAA thrombus going on to have a left atrial ablation, none had a peri-procedural stroke. The characteristics of the 3 patients with LAA thrombus are detailed in Table 2. All had $CHADS_2$ scores of ≥1, $CHA_2DS_2$-VASc scores of ≥2, impaired left ventricular systolic function (LVSF), and a peak LAA emptying velocity of <40 cm/s (23, 29 and 31 cm/s).

A univariate analysis was performed to identify associations with a peak LAA emptying velocity of <40 cm/s or LAA thrombus (Table 3). Both $CHADS_2$ and $CHA_2DS_2$-VASc scores were significantly different between patients with a peak

**Table 1** Patient Characteristics

| **Total patients (n=586)** | | | **n=** |
|---|---|---|---|
| Age (years) | | 59.9 ± 0.4 | |
| Female | | 35.5% | 208 |
| INR | | 2.3 ± 0.2 | |
| AF type | Persistent | 52.9% | 310 |
| | Paroxysmal | 47.1% | 276 |
| | (Redo procedure) | (29.8%) | (173) |
| AF at procedure | | 56.1% | 329 |
| Congestive Heart Failure | | 13.0% | 76 |
| Hypertension | | 28.0% | 164 |
| Age 65-74 | | 31.9% | 187 |
| Age >75 | | 4.3% | 25 |
| TIA/Stroke | | 3.2% | 19 |
| Vascular Disease | | 7.7% | 45 |
| $CHA^2DS_2$-VASc | 0 | 21.0% | 123 |
| | 1 | 32.1% | 188 |
| | 2 | 25.8% | 151 |
| | 3 | 13.8% | 81 |
| | 4 | 5.5% | 32 |
| | 5 | 1.9% | 11 |
| $CHADS_2$ | 0 | 42.5% | 249 |
| | 1 | 42.3% | 248 |
| | 2 | 11.1% | 65 |
| | 3 | 3.9% | 23 |
| | 4 | 0.2% | 1 |
| LA Size (cm) (n=526) | | 4.60 ± 0.04 | |
| LVSF (n=577) | Normal | 89.0% | 513 |
| | Mild | 5.2% | 30 |
| | Moderate | 3.6% | 21 |
| | Severe | 2.3% | 13 |
| **LAA Emptying Velocities <40cm/s (n=450)** | | **24.7%** | **111** |
| **LAA Thrombus** | | **0.5%** | **3** |

LAA velocity of < or >40 cm/s mainly driven by a strong association between low LAA emptying velocity/thrombus and impaired LVSF.

LA diameter was significantly greater in those with low peak LAA emptying velocity (with a significant inverse correlation r=-0.32; p<0.0001), as was the proportion of patients in persistent (as opposed to paroxysmal) AF, or in AF at the time of the procedure. Those with a high-risk $CHA_2DS_2$-VASc score ≥2 also had significantly larger LA diameter measured on TTE (4.72 ± 0.06 v's 4.48 ± 0.05 cm, p=0.001). A LA diameter >4.6cm was also identified by multivariate logistic regression

**Table 2** Individual Characteristics of Patients with an LAA Thrombus

| Age | Type of AF | AF at Procedure | INR | CHF | Hypertension | Diabetes | TIA/ Stroke | Gender | Vasc | CHA2DS2-VASc | LA Size | LAA Velocities | LVSF |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 71 | Persistent | Yes | 2.2 | Yes | No | No | No | Male | No | 2 | 4.3 | 29 | Mild |
| 56 | Paroxysmal | No | 3.3 | Yes | Yes | Yes | No | Female | No | 4 | 5.2 | 31 | Severe |
| 67 | Persistent | Yes | 2.2 | Yes | Yes | No | No | Male | No | 3 | 5.6 | 23 | Severe |

(n=389) as being independently associated with low peak LAA emptying velocity, although type of AF and congestive cardiac failure were not.

We examined the performance of different clinical criteria for identifying peak emptying velocity <40 cm/s and all LAA thombi. A combination of "LA diameter >4.6cm or $CHA_2DS_2$-VASc scores ≥1" was the simplest criteria and most sensitive (91.5% for peak LAA emptying velocity <40 cm/s, and 100% for thrombus) with the highest negative predictive value (85.5%). Although specificity was low (18.7%) this would still be a useful "rule in" criterion to put forward patients for TEE as no patients with thrombi and very few of those with low peak LAA emptying velocity at risk of thrombus would be missed in our cohort. This would reduce the number of TEEs performed by 15.9%.

## Discussion

This is the first study to use the prevalence of low LAA emptying velocity to identify those at risk of thrombus prior to left atrial catheter ablation for AF on uninterrupted warfarin therapy. We find that the prevalence of LAA thrombus is very low (0.5% of 586 patients) and generally lower than has been observed in the few studies in this area published in the last 3 years where anticoagulation has been according to $CHADS_2$ score, or where a bridging heparin strategy around the time of the procedure has mainly been used. In those treated with aspirin or warfarin according to $CHADS_2$ scoring, LAA thrombus has been reported in 1.5% of 408 patients.[12] This compares to 0.6% of 1058 patients,[13] 1.2% of 996 patients,[14] 1.6% of 585 cases, [15] 1.9% of 625 patients [16] and 3.6% of 192 patients [17] in those treated with warfarin and a bridging heparin strategy. In those where warfarin was stopped and bridging heparin was used only for high-risk patients, LAA thrombus has been reported in 3% of 329 patients.[18] Ours is the first study to evaluate the prevalence of LAA thrombus in patients who have been maintained on warfarin before, during and after the procedure (without bridging heparin), and given the low incidence of LAA thrombus and recent studies demonstrating fewer strokes and fewer major bleeding complications with this anticoagulation regime, [19, 20]this would now appear to be the gold standard for peri-procedural anticoagulation prior to LA ablation for AF.

In our series, all patients with a LAA thrombus had a low peak LAA emptying velocity (<40cm/s), impaired LVSF, and intermediate to high risk $CHADS_2$ and $CHA_2DS_2$-VASc scores. Similar clinical patient characteristics have been correlated with the occurrence of LAA thrombus regardless of anticoagulation regime, although the small number of LAA thrombi limits interpretation. In those treated with aspirin or warfarin according to $CHADS_2$ scoring, enlarged LA diameter, congestive cardiac failure, female sex, and persistent AF are significantly correlated to the occurrence of

LAA thrombus.[12] In those studies where a bridging heparin strategy was mainly used, high $CHADS_2$ scores (≥1 mainly driven by congestive cardiac failure ,[13] or >2 [15]), or individual components of the score (heart failure, hypertension and age [16]), as well as enlarged LA diameter [15-17] and structural heart disease [17] have all been correlated with the occurrence of LAA thrombus. Where warfarin was stopped prior to ablation and bridging heparin used only in high-risk patients, high $CHADS_2$ score (≥3 mainly driven by diabetes mellitus) was also correlated to the occurrence of LAA thrombus .[18]

We improve upon this approach by additionally identifying patients with low LAA velocities and performing a univariate analysis to help identify those both with thrombus and those at risk of developing thrombus. Other studies using different anticoagulation regimes prior to ablation have used criteria such as LAA sludge or spontaneous echo contrast in the LAA as risk factors for LAA thrombus. However, there is no internationally agreed definition of LAA sludge, or a consensus on how it should be managed. The appearance of spontaneous contrast in the LAA is also dependent on image quality and may or may not be present depending on the number of imaging planes in which the LAA is examined. It could be argued that it is therefore more subjective than a pulse wave doppler measurement of peak LAA emptying velocity placed 1cm into the orifice of the LAA. Our approach helps us identify with more confidence that $CHA_2DS_2$-VASc (mainly driven by CHF and impaired LVSF), persistent AF and LA diameter are key risk factors both for the presence of thrombus and risk of developing thrombus.

## Limitations

This is a pragmatic real world study and we do not have data to show that all patients maintained their target INR for at least 3 of the 6 weeks of anticoagulation prior to the procedure. In addition 22.4% of patients required low molecular weight

**Table 3** LAA Emptying Velocities <40cm/s: Univariate Analysis

| | **LAA Velocity <40 (n=111)** | | **LAA Velocity ≥40 (n=339)** | | **Univariate** Odds Ratio (95% CI) | **Univariate Analysis** or t-test |
|---|---|---|---|---|---|---|
| Age | 61.0 ± 1.0 | | 59.1 ± 0.6 | | - | NS |
| Female Gender | 38 | 34.2% | 98 | 28.9% | 1.28 (0.81-2.02) | NS |
| INR | 2.29 ± 0.04 | | 2.26 ± 0.02 | | - | NS |
| LAA Thrombus | 3 | | 0 | | - | - |
| LA Size (cm) (n=106 vs. 284) | 4.95 ± 0.09 | | 4.38 ± 0.05 | | - | *p<0.0001 |
| LA Size ≥ 4.6cm (n=106 vs. 284) | 68 | 64.2% | 98 | 34.5% | 2.40 (2.13-5.41) | p<0.0001 |
| Persistent AF | 80 | 73.0% | 169 | 49.9% | 2.60 (1.63-4.14) | *p<0.0001 |
| AF at procedure | 87 | 78.4% | 179 | 52.8% | 3.24 (1.97-5.34) | *p<0.0001 |
| $CHA_2DS_2$-VASc | 1.7 ± 0.1 | | 1.4 ± 0.1 | | - | *p<0.05 |
| $CHADS_2$ | 0.9 ± 0.1 | | 0.7 ± 0.01 | | - | *p<0.03 |
| CHF | 26 | 23.4% | 35 | 10.3% | 2.66 (1.52-4.66) | *p<0.001 |
| Mod/Sev LVSF (n=108 vs. 337) | 16 | 14.8% | 14 | 4.2% | 4.01 (1.89-8.53) | *p<0.001 |
| Hypertension | 40 | 36.0% | 116 | 34.2% | 1.08 (0.69-1.70) | NS |
| Age >75 | 4 | 3.6% | 7 | 2.1% | 1.77 (0.51-6.17) | NS |
| Age 65-74 | 39 | 35.1% | 109 | 32.2% | 1.14 (0.73-1.80) | NS |
| Diabetes | 23 | 20.7% | 52 | 15.3% | 1.44 (0.84-2.50) | NS |
| TIA/Stroke | 5 | 4.5% | 14 | 4.1% | 1.10 (0.39-3.11) | NS |
| Vascular Disease | 9 | 8.1% | 36 | 10.6% | 0.74 (0.35-1.60) | NS |

heparin following the procedure as the INR was found to be sub-therapeutic in the first 24 hours. Nevertheless whether the presence of LAA thrombus is contributed to by sub-therepeutic INR or not, in clinical practice it is not possible to be confident that every patient is within the therapeutic range all of the time and the scoring system we present remains a practical way of risk stratifying patients. TEE may not be 100% sensitive and specific for diagnosing LAA thrombus but it is currently the reference standard investigation. Importantly no peri-procedural strokes or TIAs were observed during the study suggesting that clinically significant thrombi were not missed. Newer anticoagulants such as dabigatran ,[21] apixaban [22] and rivaroxaban [23] are also becoming available which may be as good as or superior to warfarin in preventing thromboembolic events. However the peri-procedural bleeding risk of these agents around the time of left atrial ablation is not known and the ability to rapidly reverse their anticoagulant effects may limit their use in this context.

## Conclusions

Whilst the 2012 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society statement [2] encourages pre-procedural TEE to screen for the presence of thrombus in patients undergoing left atrial ablation of AF, it acknowledges that there is a lack of consensus or data especially in patients that have been maintained on therapeutic oral anticoagulation. We find that in patients maintained on uninterrupted warfarin therapy prior to AF ablation, the incidence of LAA thrombus is very low. Based on our data and the risk factors we identify for LAA thrombus or low LAA emptying velocity, we propose that peri-operative TEE may only need to be performed in patients with $CHA_2DS_2$-VASc scores of 1 or above, or if LA diameter is >4.6cm on TTE providing patients have been therapeutically anticoagulated. This approach has a 100% sensitivity for identifying thrombus in addition to a 91.5% sensitivity for identifying those at risk of thrombus with a peak LAA velocity of <40cm/s and could better target pre-procedural TEEs where resources are limited. Such a scheme should be validated in a large prospective study.

## Disclosures

No disclosures relevant to this article were made by the authors.

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