Left Atrial Appendage Occlusion
vs.
Anticoagulation

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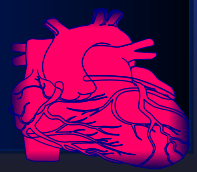

Kenneth Tobin, D.O., FACC, FACOI

I have no disclosures

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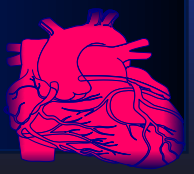
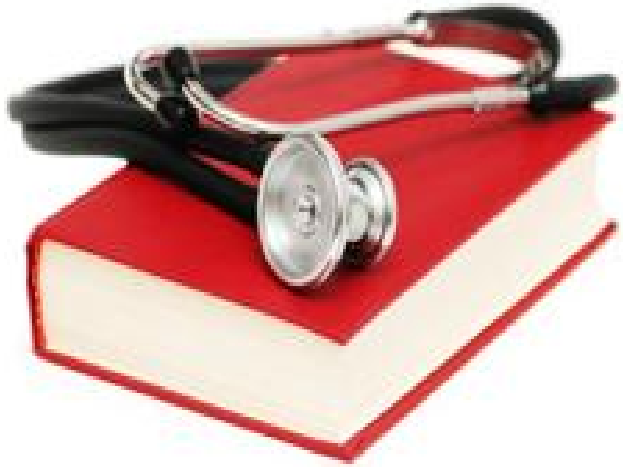


A 46 year old male patient is in for an annual physical exam. What is his lifetime risk of developing AF?

1. 1%
2. 5%
3. 10%
4. 25%



Incidence of AF

Lifetime Risk for AF at Selected Index Ages by Sex

Index Age, yrs	Men	Women
40	**26.0%** (24.0 – 27.0)	**23.0%** (21.0 – 24.0)
50	**25.9%** (23.9 – 27.0)	**23.2%** (21.3 – 24.3)
60	**25.8%** (23.7 – 26.9)	**23.4%** (21.4 – 24.4)
70	**24.3%** (22.1 – 25.5)	**23.0%** (20.9 – 24.1)
80	**22.7%** (20.1 – 24.1)	**21.6%** (19.3 – 22.7)

1 in 4

Men & women ≥40 Years will develop AF

Lifetime risk if currently free of AF

Anticoagulation FORUM

BOSTON UNIVERSITY

Lloyd-Jones DM, et al. Circulation. 2004 Aug 31;110(9):1042-6. Pub Med PMID: 15313941.

Atrial Fibrillation and Stroke

Scoring Differences Between $CHADS_2$ and CHA_2DS_2-VASc

Risk Factor	$CHADS_2$ (Maximum score, 6) Points	CHA_2DS_2-VASc (Maximum score, 9) Points
Congestive heart failure	1	1
Hypertension	1	1
Diabetes	1	1
Vascular disease	N/A	1
Age 65-74	N/A	1
Age ≥75	1	2
Female sex	N/A	1
Previous stroke/TIA	2	2

N/A – not applicable

Journal WATCH

Excellence

Atrial Fibrillation and Stroke

$CHADS_2$ score and stroke risk

Risk factor	Points
C - Congestive heart failure	1
H - Hypertension	1
A - Age >75 years	1
D - Diabetes	1
S - Prior Stroke or TIA	2

$CHADS_2$ score	Stroke rate per 100 patient-years
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

Gage BF et al. JAMA 2001;285(22):2864-2870.

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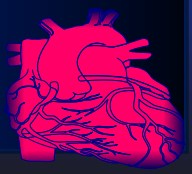

$CHADS_2$–VASc Stroke Risk	
$CHADS_2$-VASc Score	Stroke Risk %
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

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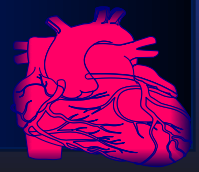
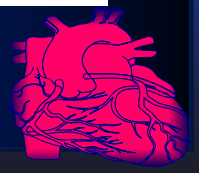


Bleeding Risk Scores in AF

ATRIA		HAS-BLED		HEMORR$_2$HAGES	
Anemia[1]	3	Hypertension[4]	1	Hepatic[10] or Renal disease[2]	1 1
Severe renal disease[2]	3	Abnormal Renal[5] or Liver function[6]	1 1	Ethanol abuse	1
Age ≥75 yrs	2	Stroke	1	Malignancy	1
Any prior hemorrhage	1	Bleeding	1	Older Age (>75 yrs)	1
Hypertension[3]	1	Labile INR[8]	1	Reduced platelet number or function[11]	1
		Elderly (>65 yrs)	1	Rebleeding[12]	2
		Drugs[9] or Alcohol	1 1	Hypertension[4]	1
				Anemia[13]	1
				Genetic factors[14]	1
				Excessive fall risk[15]	1
				Stroke	1

1. Hemoglobin <13 g/dl men; <12 g/dl women
2. Estimated glomerular filtration rate <30 ml/min or dialysis-dependent
3. Diagnosed hypertension
4. Systolic blood pressure >160 mmHg
5. Presence of chronic dialysis or renal transplantation or serum creatinine ≥200 mmol/L
6. Chronic hepatic disease (eg cirrhosis) or biochemical evidence of significant hepatic derangement (eg bilirubin 2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal, etc.)
8. Unstable/high INRs or poor time in therapeutic range (eg <60%)
9. Concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse etc.
10. Cirrhosis, two-fold or greater elevation of AST or APT, or albumin <3.6 g/dl
11. Platelets <75,000, use of antiplatelet therapy (eg daily aspirin) or NSAID therapy; or blood dyscrasia
12. Prior hospitalization for bleeding
13. Most recent hematocrit <30 or hemoglobin <10 g/dl
14. CYP2C9*2 and/or CYP2C9*3
15. Alzheimer's dementia, Parkinson's disease, schizophrenia, or any condition predisposing to repeated falls

Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. J Am Coll Cardiol 2012;60:000–000. 2012 Jul 24. [Epub ahead of print] Online Appendix. PMID: 22858389.



THE PROBLEM

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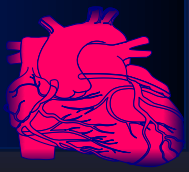

- **1 in 10 patients have a contraindication to oral anticoagulation**
- **1 on 5 patients in randomized clinical trials for AF/Stroke prevention discontinued their NOACs**
- **Nearly 40% of AF patients do not receive appropriate anticoagulation rx due to:**
  - ***Contraindication***
  - ***Bleeding issues***
  - ***Patient/physician preferences***

Kakkar AK, Mueller I Bassand JP, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. PLoS One 2013;8:e63479

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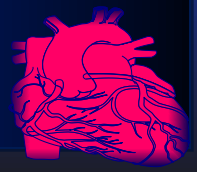
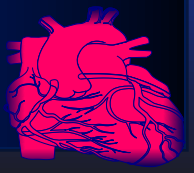


Reasons for Withholding OAC in Patients with AF and Stroke Risk

	Patient	Provider	System
Appropriate:	Refusal after complete understanding	Recent intracranial hemorrhage	Lack of access to INR monitoring and can not afford novel drug
Inappropriate:	Desire to avoid monitoring (and can afford NOAC)	Old age; CHADS score = 1	Lack of time to address issues
Uncertain appropriateness:	Desire to avoid bruising	Substantial fall risk	Unable to afford cost of monitoring



Cardioembolic Events in Atrial Fibrillation

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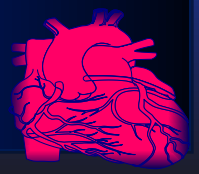

Atrial Fibrillation and Stroke

- The LAA is a remnant of the embryologic left atrium (the rest of the left atrium is an outgrowth of the pulmonary veins)
- The LAA has different embryologic, anatomic, and pathophysiologic features from the left atrium
  - *The LAA seems to play an important role in the regulation of heart rate and fluid balance*
- LAA thrombus is present in up to 15% of pts with AF
- In non-valvular AF, 90% of thrombi are located in the LAA

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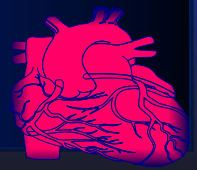
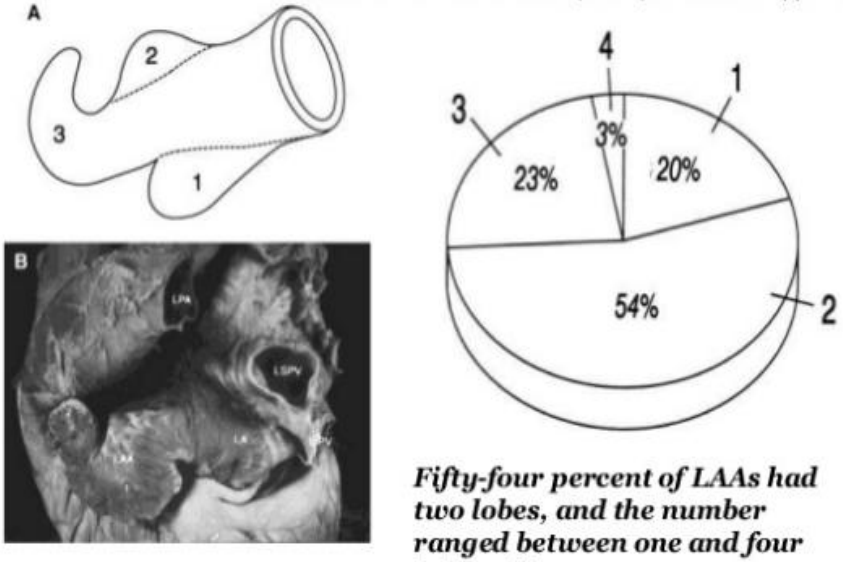


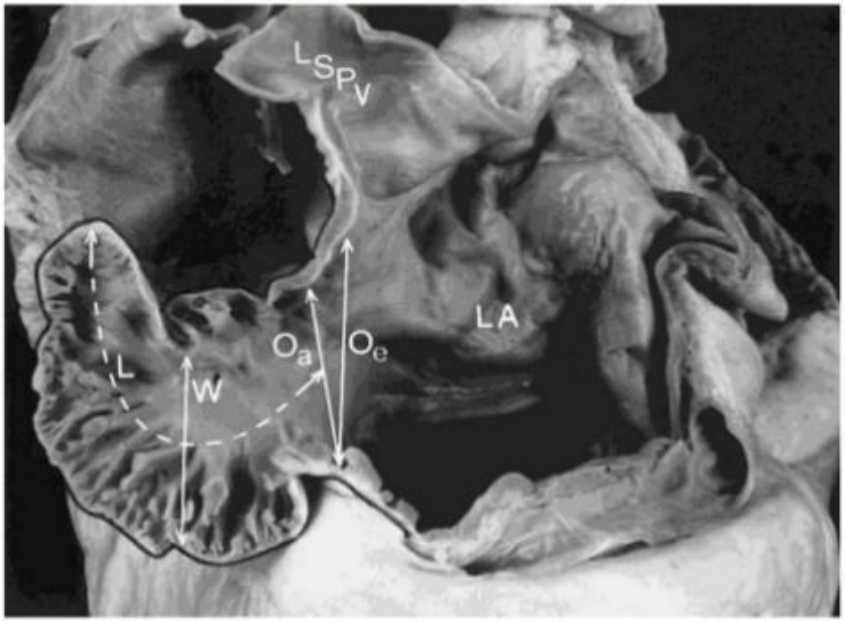
Distribution of number of lobes (1 to 4) of left atrial appendage



Fifty-four percent of LAAs had two lobes, and the number ranged between one and four lobes . There were no age or sex differences

Veinot J et al. Circulation 1997;96:3112-3115

ANATOMY OF LAA



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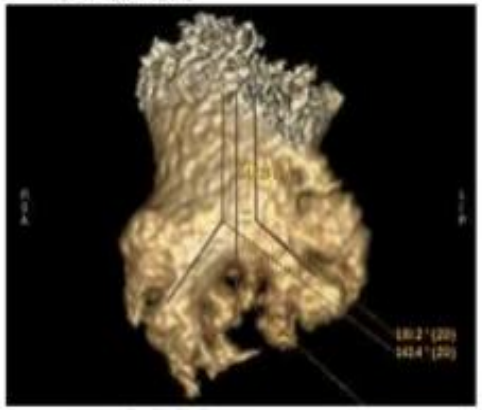
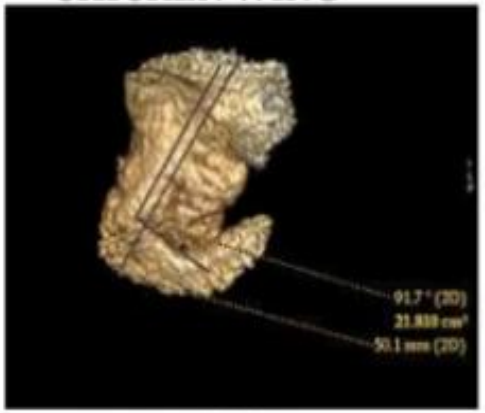
4 MORPHOLOGICAL TYPES

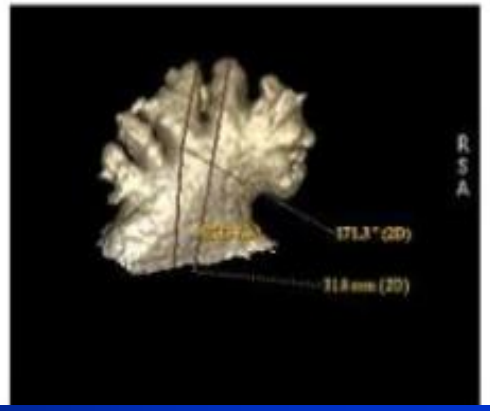
CACTUS



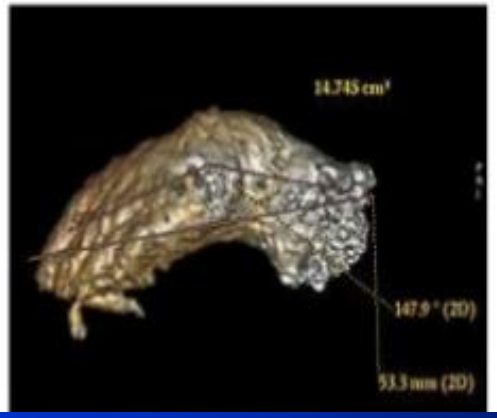
CHICKEN WING



BROCCOLI



WINDSOCK



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A POTENTIAL SOLUTION

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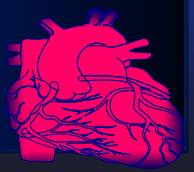

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CLINICAL RESEARCH **Clinical Trials**

Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO System) to Prevent Stroke in High-Risk Patients With Non-Rheumatic Atrial Fibrillation

Results From the International Multi-Center Feasibility Trials

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OBJECTIVES These studies were conducted to evaluate the feasibility of percutaneous left atrial appendage (LAA) occlusion using the PLAATO system (ev3 Inc., Plymouth, Minnesota).

BACKGROUND Patients with atrial fibrillation (AF) have a five-fold increased risk for stroke. Other studies have shown that more than 90% of atrial thrombi in patients with non-rheumatic AF originate in the LAA. Transvenous closure of the LAA is a new approach in preventing embolism in these patients.

METHODS Within two prospective, multi-center trials, LAA occlusion was attempted in 111 patients (age 71 ± 9 years). All patients had a contraindication for anticoagulation therapy and at least one additional risk factor for stroke. The primary end point was incidence of major adverse events (MAEs), a composite of stroke, cardiac or neurological death, myocardial infarction, and requirement for procedure-related cardiovascular surgery within the first month.

RESULTS Implantation was successful in 108 of 111 patients (97.3%, 95% confidence interval [CI] 92.3% to 99.4%) who underwent 113 procedures. One patient (0.9%, 95% CI 0.02% to 4.9%) experienced two MAEs within the first 30 days: need for cardiovascular surgery and in-hospital neurological death. Three other patients underwent in-hospital pericardiocentesis due to a hemopericardium. Average follow-up was 9.8 months. Two patients experienced stroke. No migration or mobile thrombus was noted on transesophageal echocardiogram at one and six months after device implantation.

CONCLUSIONS Closing the LAA using the PLAATO system is feasible and can be performed at acceptable risk. It may become an alternative in patients with AF and a contraindication for lifelong anticoagulation treatment. (J Am Coll Cardiol 2005;46:9–14) © 2005 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is responsible for more than 15% of all strokes (1–3). Besides irregular heart rate and possible lowered endurance, AF leads to insufficient contraction of the left atrium. Stagnation of blood flow within the left atrium leads to hypercoagulability and thus to an increased risk for thrombus formation (4). Several surgical, echocardiographic, and autopsy studies have shown that more than 90% of all thrombi in patients with non-rheumatic AF forming in the left atrium

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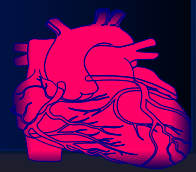
- ✓ **111 patients with contraindications to anticoagulation**
- ✓ **Feasibility study - 2005**
- ✓ **Reasonable results with noted complications of tamponade and device embolization**
- ✓ **Device not pursued further due to financial considerations**



Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial

David R Holmes, Vivek Y Reddy, Zaldon G Turi, Shephal K Doshi, Horst Sievert, Maurice Buchbinder, Christopher M Mullin, Peter Sick, for the PROTECT AF Investigators*

Lancet 2009; 374: 534–42
See Editorial page 518
See Comment page 520

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Summary

Background In patients with non-valvular atrial fibrillation, embolic stroke is thought to be associated with left atrial appendage (LAA) thrombi. We assessed the efficacy and safety of percutaneous closure of the LAA for prevention of stroke compared with warfarin treatment in patients with atrial fibrillation.

Methods Adult patients with non-valvular atrial fibrillation were eligible for inclusion in this multicentre, randomised non-inferiority trial if they had at least one of the following: previous stroke or transient ischaemic attack, congestive heart failure, diabetes, hypertension, or were 75 years or older. 707 eligible patients were randomly assigned in a 2:1 ratio by computer-generated randomisation sequence to percutaneous closure of the LAA and subsequent discontinuation of warfarin (intervention; n=463) or to warfarin treatment with a target international normalised ratio between 2·0 and 3·0 (control; n=244). Efficacy was assessed by a primary composite endpoint of stroke, cardiovascular death, and systemic embolism. We selected a one-sided probability criterion of non-inferiority for the intervention of at least 97·5%, by use of a two-fold non-inferiority margin. Serious adverse events that constituted the primary endpoint for safety included major bleeding, pericardial effusion, and device embolisation. Analysis was by intention to treat. This study is registered with Clinicaltrials.gov, number NCT00129545.

Findings At 1065 patient-years of follow-up, the primary efficacy event rate was 3·0 per 100 patient-years (95% credible interval [CrI] 1·9–4·5) in the intervention group and 4·9 per 100 patient-years (2·8–7·1) in the control group (rate ratio [RR] 0·62, 95% CrI 0·35–1·25). The probability of non-inferiority of the intervention was more than 99·9%. Primary safety events were more frequent in the intervention group than in the control group (7·4 per 100 patient-years, 95% CrI 5·5–9·7, *vs* 4·4 per 100 patient-years, 95% CrI 2·5–6·7; RR 1·69, 1·01–3·19).

Interpretation The efficacy of percutaneous closure of the LAA with this device was non-inferior to that of warfarin therapy. Although there was a higher rate of adverse safety events in the intervention group than in the control group, events in the intervention group were mainly a result of periprocedural complications. Closure of the LAA might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with non-valvular atrial fibrillation.

Funding AtriTech.

Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia, affecting an estimated 6 million individuals in the USA.[1] Since atrial fibrillation mainly affects elderly people, its prevalence is expected to increase in parallel with the increasing age of the population, with a predicted 15·9 million cases by 2050.[1,2] The lifetime risk for development of atrial fibrillation is one in four in men and women 40 years of age and older.[3] Stroke, the most serious complication of atrial fibrillation, occurs in 5% of non-anticoagulated patients every year. The risk of stroke increases substantially with age, from 1·5% in individuals aged 50–59 years to 23·5% for those aged 80–89 years.[3–5] Stroke is the third most frequent cause of death in the USA and the leading cause of serious disability. Therefore, stroke prophylaxis is a crucial component of management of atrial fibrillation.

Although membrane-active antiarrhythmic drugs[6–12] and catheter ablation provide symptomatic relief for patients with atrial fibrillation, neither method is sufficiently reliable in preventing thromboembolic events, and long-term oral anticoagulation therapy is recommended irrespective of the rhythm management strategy. Randomised controlled trials have shown that warfarin is effective in preventing stroke, more so than aspirin and combination aspirin-clopidogrel.[13–15] Despite its proven efficacy, warfarin is often not well tolerated by patients, has a very narrow therapeutic range, and has a high risk for bleeding complications.[16] Furthermore, the effectiveness of anticoagulation varies because of interactions with some foods and other medications; even with frequent monitoring and dose adjustments, patients' test results are outside of the therapeutic range in up to half of all blood drawings.[17] Partly for these reasons, only around 50% of patients

- ✓ 707 pts randomized 2:1 to the Watchman device vs Coumadin: Chads2 ≥ 1
- ✓ Designed as a non-inferiority trial
- ✓ Composite primary efficacy endpoint of stroke, systemic embolism, or cardiovascular/unexplained death was not different between the two treatment arms

Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial

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Methods Adult patients with non-valvular atrial fibrillation were eligible for inclusion in this multicentre, randomised non-inferiority trial if they had at least one of the following: previous stroke or transient ischaemic attack, congestive heart failure, diabetes, hypertension, or were 75 years or older. 707 eligible patients were randomly assigned in a 2:1 ratio by computer-generated randomisation sequence to percutaneous closure of the LAA and subsequent discontinuation of warfarin (intervention; n=463) or to warfarin treatment with a target international normalised ratio between 2·0 and 3·0 (control; n=244). Efficacy was assessed by a primary composite endpoint of stroke, cardiovascular death, and systemic embolism. We selected a one-sided probability criterion of non-inferiority for the intervention of at least 97·5%, by use of a two-fold non-inferiority margin. Serious adverse events that constituted the primary endpoint for safety included major bleeding, pericardial effusion, and device embolisation. Analysis was by intention to treat. This study is registered with Clinicaltrials.gov, number NCT00129545.

Findings At 1065 patient-years of follow-up, the primary efficacy event rate was 1·0 per 100 patient-years (95% credible interval [CrI] 1·9–4·5) in the intervention group and 4·9 per 100 patient-years (2·8–7·1) in the control group (rate ratio [RR] 0·62, 95% CrI 0·35–1·25). The probability of non-inferiority of the intervention was more than 99·9%. Primary safety events were more frequent in the intervention group than in the control group (7·4 per 100 patient-years, 95% CrI 5·5–9·7, *vs* 4·4 per 100 patient-years, 95% CrI 2·5–6·7; RR 1·69, 1·01–3·39).

Interpretation The efficacy of percutaneous closure of the LAA with this device was non-inferior to that of warfarin therapy. Although there was a higher rate of adverse safety events in the intervention group than in the control group, events in the intervention group were mainly a result of periprocedural complications. Closure of the LAA might provide an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with non-valvular atrial fibrillation.

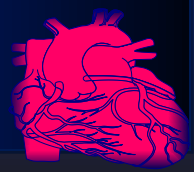
Funding Atritech.

Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia, affecting an estimated 6 million individuals in the USA.[1] Since atrial fibrillation mainly affects elderly people, its prevalence is expected to increase in parallel with the increasing age of the population, with a predicted 15·9 million cases by 2050.[1,2] The lifetime risk for development of atrial fibrillation is one in four in men and women 40 years of age and older.[3] Stroke, the most serious complication of atrial fibrillation, occurs in 5% of non-anticoagulated patients every year. The risk of stroke increases substantially with age, from 1·5% in individuals aged 50–59 years to 23·5% for those aged 80–89 years.[3,4] Stroke is the third most frequent cause of death in the USA and the leading cause of serious disability. Therefore, stroke prophylaxis is a crucial component of management of atrial fibrillation.

Although membrane-active antiarrhythmic drugs[5–7] and catheter ablation provide symptomatic relief for patients with atrial fibrillation, neither method is sufficiently reliable in preventing thromboembolic events, and long-term oral anticoagulation therapy is recommended irrespective of the rhythm management strategy. Randomised controlled trials have shown that warfarin is effective in preventing stroke, more so than aspirin and combination aspirin-clopidogrel.[8–10] Despite its proven efficacy, warfarin is often not well tolerated by patients, has a very narrow therapeutic range, and has a high risk for bleeding complications.[11] Furthermore, the effectiveness of anticoagulation varies because of interactions with some foods and other medications; even with frequent monitoring and dose adjustments, patients' test results are outside of the therapeutic range in up to half of all blood drawings.[12] Partly for these reasons, only around 50% of patients

- ✓ Device arm were placed on warfarin + ASA for 45 days post implant followed by repeat TEE
- ✓ Warfarin discontinued if LAA was completely closed or there was < 5 mm gap
- ✓ ASA + Plavix for 6 months followed by ASA alone
- ✓ Probability of non-inferiority was > 99.9%



Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial

David R Holmes, Vivek Y Reddy, Zoltan G Turi, Shephal K Doshi, Horst Sievert, Mauricio Buchbinder, Christopher M Mullin, Peter Sick, for the PROTECT AF Investigators*

Lancet 2009; 374: 534–42
See Editorial page 512
See Comment page 514

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Summary

Background In patients with non-valvular atrial fibrillation, embolic stroke is thought to be associated with left atrial appendage (LAA) thrombi. We assessed the efficacy and safety of percutaneous closure of the LAA for prevention of stroke compared with warfarin treatment in patients with atrial fibrillation.

Methods Adult patients with non-valvular atrial fibrillation were eligible for inclusion in this multicentre, randomised non-inferiority trial if they had at least one of the following: previous stroke or transient ischaemic attack, congestive heart failure, diabetes, hypertension, or were 75 years or older. 707 eligible patients were randomly assigned in a 2:1 ratio by computer-generated randomisation sequence to percutaneous closure of the LAA and subsequent discontinuation of warfarin (intervention; n=463) or to warfarin treatment with a target international normalised ratio between 2·0 and 3·0 (control; n=244). Efficacy was assessed by a primary composite endpoint of stroke, cardiovascular death, and systemic embolism. We selected a one-sided probability criterion of non-inferiority for the intervention of at least 97·5%, by use of a two-fold non-inferiority margin. Serious adverse events that constituted the primary endpoint for safety included major bleeding, pericardial effusion, and device embolization. Analysis was by intention to treat. This study is registered with Clinicaltrials.gov, number NCT00129545.

Findings At 1065 patient-years of follow-up, the primary efficacy event rate was 3·0 per 100 patient-years (95% credible interval [CrI] 1·9–4·5) in the intervention group and 4·9 per 100 patient-years (2·8–7·1) in the control group (rate ratio [RR] 0·62, 95% CrI 0·35–1·25). The probability of non-inferiority of the intervention was more than 99·9%. Primary safety events were more frequent in the intervention group than in the control group (7·4 per 100 patient-years, 95% CrI 5·5–9·7, *vs* 4·4 per 100 patient-years, 95% CrI 2·5–6·7; RR 1·69, 1·01–3·39).

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Funding AtriTech.

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Atrial fibrillation is the most common sustained cardiac arrhythmia, affecting an estimated 6 million individuals in the USA.[1] Since atrial fibrillation mainly affects elderly people, its prevalence is expected to increase in parallel with the increasing age of the population, with a predicted 15·9 million cases by 2050.[1,2] The lifetime risk for development of atrial fibrillation is one in four in men and women 40 years of age and older.[3] Stroke, the most serious complication of atrial fibrillation, occurs in 5% of non-anticoagulated patients every year. The risk of stroke increases substantially with age, from 1·5% in individuals aged 50–59 years to 23·5% for those aged 80–89 years.[3,4] Stroke is the third most frequent cause of death in the USA and the leading cause of serious disability. Therefore, stroke prophylaxis is a crucial component of management of atrial fibrillation.

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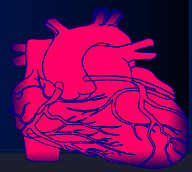
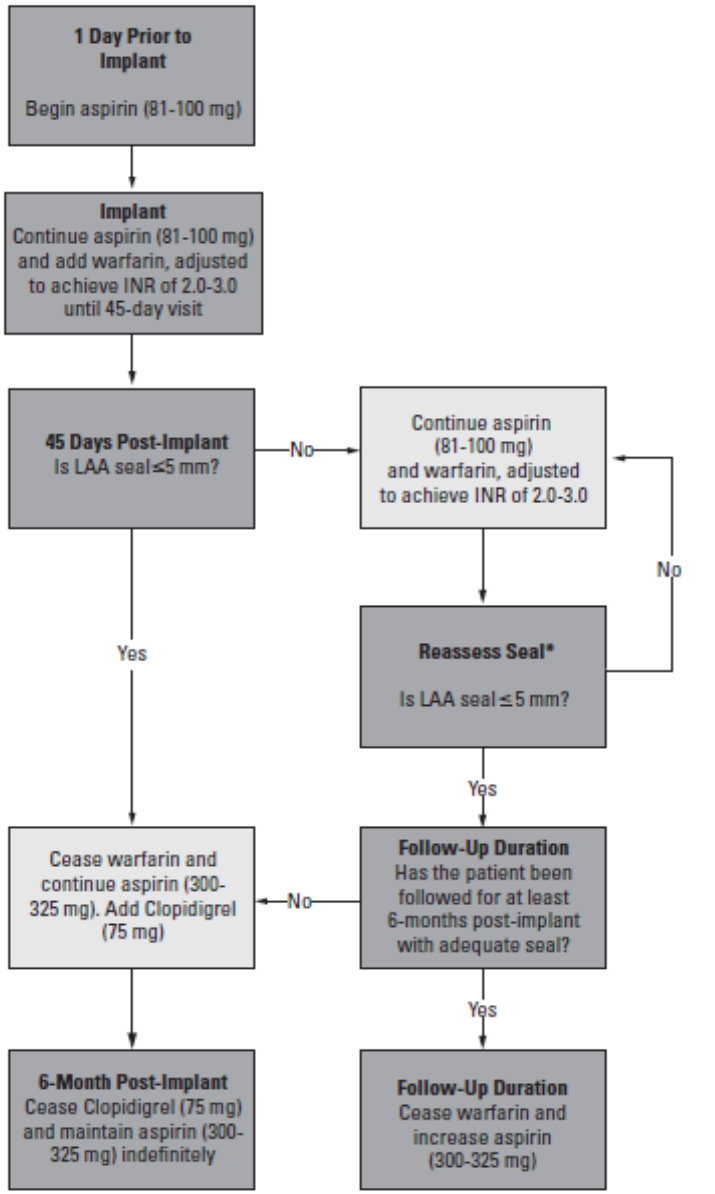
Excellence

- ✓ Early safety event rates were higher with the device 1.69 at 1065 patient years
- ✓ Serious pericardial effusion 4.8%
- ✓ Procedural ischemic stroke 1.1%
- ✓ The robustness was tempered by:
  - (a) the low risk population as the Chads2 for inclusion was ≥1
  - (b) Number of subjects who did not receive protocol treatment per randomization
  - (c) Higher than expected hemorrhagic stroke rate in the Warfarin group
- ✓ Thus – the FAD required second RCT to confirm the safety/effectiveness in a higher risk cohort





*The Performance and timing of TEE to re-evaluate the LAA seal is left to physician discretion.

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ORIGINAL INVESTIGATIONS

Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy

The PREVAIL Trial

David R. Holmes Jr, MD,* Saibal Kar, MD,† Matthew J. Price, MD,‡ Brian Whisenant, MD,§ Horst Sievert, MD,‖ Shephal K. Doshi, MD,¶ Kenneth Huber, MD,# Vivek Y. Reddy, MD**

ABSTRACT

BACKGROUND In the PROTECT AF (Watchman Left Atrial Appendage Closure Technology for Embolic Protection in Patients With Atrial Fibrillation) trial that evaluated patients with nonvalvular atrial fibrillation (NVAF), left atrial appendage (LAA) occlusion was noninferior to warfarin for stroke prevention, but a periprocedural safety hazard was identified.

OBJECTIVES The goal of this study was to assess the safety and efficacy of LAA occlusion for stroke prevention in patients with NVAF compared with long-term warfarin therapy.

METHODS This randomized trial further assessed the efficacy and safety of the Watchman device. Patients with NVAF who had a $CHADS_2$ (congestive heart failure, hypertension, age >75 years, diabetes mellitus, and previous stroke/transient ischemic attack) score ≥2 or 1 and another risk factor were eligible. Patients were randomly assigned (in a 2:1 ratio) to undergo LAA occlusion and subsequent discontinuation of warfarin (intervention group, n = 269) or receive chronic warfarin therapy (control group, n = 138). Two efficacy and 1 safety coprimary endpoints were assessed.

RESULTS At 18 months, the rate of the first coprimary efficacy endpoint (composite of stroke, systemic embolism [SE], and cardiovascular/unexplained death) was 0.064 in the device group versus 0.063 in the control group (rate ratio 1.07 [95% credible interval (CrI): 0.57 to 1.89]) and did not achieve the prespecified criteria noninferiority (upper boundary of 95% CrI ≥1.75). The rate for the second coprimary efficacy endpoint (stroke or SE >7 days' postrandomization) was 0.0253 versus 0.0200 (risk difference 0.0053 [95% CrI: −0.0190 to 0.0273]), achieving noninferiority. Early safety events occurred in 2.2% of the Watchman arm, significantly lower than in PROTECT AF, satisfying the pre-specified safety performance goal. Using a broader, more inclusive definition of adverse effects, these still were lower in PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial than in PROTECT AF (4.2% vs. 8.7%; p = 0.004). Pericardial effusions requiring surgical repair decreased from 1.6% to 0.4% (p = 0.027), and those requiring pericardiocentesis decreased from 2.9% to 1.5% (p = 0.36), although the number of events was small.

CONCLUSIONS In this trial, LAA occlusion was noninferior to warfarin for ischemic stroke prevention or SE >7 days' post-procedure. Although noninferiority was not achieved for overall efficacy, event rates were low and numerically comparable in both arms. Procedural safety has significantly improved. This trial provides additional data that LAA occlusion is a reasonable alternative to warfarin therapy for stroke prevention in patients with NVAF who do not have an absolute contraindication to short-term warfarin therapy. (J Am Coll Cardiol 2014;64:1-12) © 2014 by the American College of Cardiology Foundation.

From the *Mayo Clinic, Rochester, Minnesota; †Cedars Sinai Medical Center, Los Angeles, California; ‡Scripps Clinic, La Jolla, California; §Intermountain Medical Center, Salt Lake City, Utah; ‖Cardiovasculares Centrum, Frankfurt, Germany; ¶Pacific Heart Institute, Santa Monica, California; #Saint Luke's Mid America Heart Institute, Kansas City, Missouri; and the **Mount Sinai

- ✓ Chads2 ≥ 2 (or > 1 and one additional high risk component)

- ✓ 3 primary endpoints:

(a) Composite of stroke, SE, and cardiovascular/unexplained death

(b) Ischemic stroke and SE 7 days post implant

(c) Early safety composite endpoint

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ORIGINAL INVESTIGATIONS

Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long-Term Warfarin Therapy

The PREVAIL Trial

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Excellence

- ✓ 407 patients
- ✓ 18 month first co-primary endpoint *did not* meet noninferiority criteria
- ✓ 18 month second co-primary endpoint (ischemic efficacy 7 days post procedure) *did* meet noninferiority criteria
- ✓ Early safety data also chanced pre-specified safety performance goals

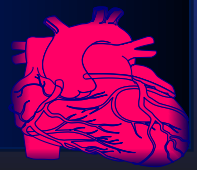

TABLE 1 Patient Demographics

	PROTECT AF			PREVAIL			Combined Cohort		
	Device (n = 463)	Control (n = 244)	p Value	Device (n = 269)	Control (n = 138)	p Value	Device (n = 732)	Control (n = 382)	p Value
Age, yrs	71.7 ± 8.8	72.7 ± 9.2	0.18	74.0 ± 7.4	74.9 ± 7.2	0.26	72.6 ± 8.4	73.5 ± 8.6	0.09
Male	70.4	70.1	0.93	67.7	74.6	0.15	69.4	71.7	0.42
$CHADS_2$ score	2.2 ± 1.2	2.3 ± 1.2	0.07	2.6 ± 1.0	2.6 ± 1.0	0.48	2.3 ± 1.1	2.4 ± 1.2	0.06
Risk factors									
CHF	26.8	27.0	0.94	23.4	23.2	0.96	25.5	25.7	0.97
Hypertension	89.6	90.2	0.82	88.5	97.1	0.003	89.2	92.7	0.06
Age ≥75 yrs	36.9	41.4	0.25	46.5	46.4	0.99	40.4	43.2	0.38
Diabetes	24.4	29.5	0.14	33.8	29.7	0.40	27.9	29.6	0.55
Prior stroke/TIA	17.7	20.1	0.44	29.7	29.7	1.00	22.1	23.6	0.59
CHA_2DS_2-VASc score	3.4 ± 1.5	3.7 ± 1.6	0.02	4.0 ± 1.2	4.1 ± 1.2	0.4	3.6 ± 1.4	3.9 ± 1.5	0.02
AF pattern									
Paroxysmal	43.2	40.6	0.50	48.7	51.4	0.60	45.2	44.5	0.82
Persistent	21.0	20.5	0.89	31.6	28.3	0.49	24.9	23.3	0.56
Permanent	34.6	38.1	0.35	15.6	15.9	0.93	27.6	30.1	0.38
Unknown	1.3	0.8	0.72	1.5	0.7	0.50	1.4	0.8	0.56
Paced	0	0	—	2.6	3.6	0.55	1.0	1.3	0.56

Values are mean ± SD or %.

$CHADS_2$ = congestive heart failure, hypertension, 75 years of age or older, diabetes mellitus, and previous stroke or transient ischemic attack; CHA_2DS_2-VASc = congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65 to 74 years of age, female; CHF = congestive heart failure; PREVAIL = Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy; PROTECT AF = WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation; TIA = transient ischemic attack.

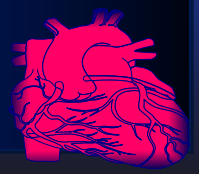

TABLE 7 Comparison of Outcomes in Device Patients in PROTECT AF, CAP, and PREVAIL

	PROTECT AF	CAP	PREVAIL	p Value
Implant success	90.9	94.3	95.1	0.04
All 7-day procedural complications	8.7	4.2	4.5	0.004
Pericardial effusion requiring surgery	1.6	0.2	0.4	0.03
Pericardial effusion with pericardiocentesis	2.4	1.2	1.5	0.318
Procedure-related strokes	1.1	0.0	0.7	0.02
Device embolization	0.4	0.2	0.7	0.368

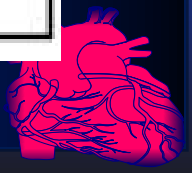

TABLE 6 Demographic Characteristics of Patients Receiving the Watchman Device in PROTECT AF, CAP, and PREVAIL

	PROTECT AF (n = 463)	CAP (n = 566)	PREVAIL (n = 269)	p Value
Age, yrs	71.7 ± 8.8 (46.0, 95.0)	74.0 ± 8.3 (44.0, 94.0)	74.0 ± 7.4 (50.0, 94.0)	<0.001
Male	326/463 (70.4%)	371/566 (65.5%)	182/269 (67.7%)	0.252
$CHADS_2$ score (continuous)	2.2 ± 1.2 (1.0, 6.0)	2.5 ± 1.2 (1.0, 6.0)	2.6 ± 1.0 (1.0, 6.0)	<0.001
$CHADS_2$ risk factors				
CHF	124/463 (26.8%)	108/566 (19.1%)	63/269 (23.4%)	
Hypertension	415/463 (89.6%)	503/566 (88.9%)	238/269 (88.5%)	
Age ≥75 yrs	190/463 (41.0%)	293/566 (51.8%)	140/269 (52.0%)	
Diabetes	113/463 (24.4%)	141/566 (24.9%)	91/269 (33.8%)	
Stroke/TIA	82/463 (17.7%)	172/566 (30.4%)	74/269 (27.5%)	

Values are mean ± SD (minimum, maximum) or n/N (%).

CAP = Continued Access PROTECT AF; PROTECT AF = Watchman Left Atrial Appendage Closure Technology for Embolic Protection in Patients With Atrial Fibrillation; other abbreviation as in Tables 1 and 3.

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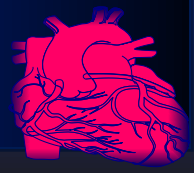

News Releases

Boston Scientific Receives FDA Approval for WATCHMAN™ Left Atrial Appendage Closure Device

First-Of-Its-Kind Alternative to Long-Term Warfarin Therapy for Stroke Risk Reduction in Patients with Non-Valvular Atrial Fibrillation

MARLBOROUGH, Mass., March 13, 2015 /**PRNewswire**/ -- Boston Scientific Corporation (NYSE: BSX) has received U.S. Food and Drug Administration (FDA) approval for the WATCHMAN Left Atrial Appendage Closure Device. The WATCHMAN Device offers a new stroke risk reduction option for high-risk patients with non-valvular atrial fibrillation who are seeking an alternative to long-term warfarin therapy. The WATCHMAN Device will be made available to U.S. centers involved in our clinical studies and additional, specialized centers as physicians are trained on the implant procedure.

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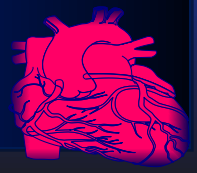

5-Year Outcomes After Left Atrial Appendage Closure

From the PREVAIL and PROTECT AF Trials

Vivek Y. Reddy, MD,[*†] Shephal K. Doshi, MD,[*] Saibal Kar, MD,[‡] Douglas N. Gibson, MD,[§] Matthew J. Price, MD,[‖] Kenneth Stein, MD,[¶] Rodney P. Horton, MD,[#] Maurice Buchbinder, MD,[**] Petr Neuzil, MD, PhD,[††] Nicole T. Gordon, BSEE,[‡] David R. Holmes, Jr, MD,[‡] on Behalf of the PREVAIL and PROTECT AF Investigators

ABSTRACT

BACKGROUND The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial demonstrated that left atrial appendage closure (LAAC) with the Watchman device (Boston Scientific, St. Paul, Minnesota) was equivalent to warfarin for preventing stroke in atrial fibrillation, but had a high rate of complications. In a second randomized trial, PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy), the complication rate was low. The warfarin cohort experienced an unexpectedly low ischemic stroke rate, rendering the efficacy endpoints inconclusive. However, these outcomes were based on relatively few patients followed for a relatively short time.

OBJECTIVES The final results of the PREVAIL trial, both alone and as part of a patient-level meta-analysis with the PROTECT AF trial, are reported with patients in both trials followed for 5 years.

METHODS PREVAIL and PROTECT AF are prospective randomized clinical trials with patients randomized 2:1 to LAAC or warfarin; together, they enrolled 1,114 patients for 4,343 patient-years. Analyses are by intention-to-treat, and rates are events per 100 patient-years.

RESULTS For the PREVAIL trial, the first composite coprimary endpoint of stroke, systemic embolism (SE), or cardiovascular/unexplained death did not achieve noninferiority (posterior probability for noninferiority = 88.4%), whereas the second coprimary endpoint of post-procedure ischemic stroke/SE did achieve noninferiority (posterior probability for noninferiority = 97.5%); the warfarin arm maintained an unusually low ischemic stroke rate (0.79%). In the meta-analysis, the composite endpoint was similar between groups (hazard ratio [HR]: 0.820; p = 0.37), as were all-stroke/SE (HR: 0.90; p = 0.87). The ischemic stroke/SE rate was numerically higher with LAAC, but this difference did not reach statistical significance (HR: 1.71; p = 0.080). However, differences in hemorrhagic stroke, disabling/fatal stroke, cardiovascular/unexplained death, all-cause death, and post-procedure bleeding favored LAAC (HR: 0.20; p = 0.0002; HR: 0.45; p = 0.03; HR: 0.59; p = 0.027; HR: 0.73; p = 0.035; HR: 0.48; p = 0.0003, respectively).

CONCLUSIONS These 5-year outcomes of the PREVAIL trial, combined with the 5-year outcomes of the PROTECT AF trial, demonstrate that LAAC with Watchman provides stroke prevention in nonvalvular atrial fibrillation comparable to warfarin, with additional reductions in major bleeding, particularly hemorrhagic stroke, and mortality. (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation; NCT00129649; and Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy; NCT00832442) (J Am Coll Cardiol 2017;70:2964–75) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [*]Department of Cardiology, Icahn School of Medicine at Mount Sinai, New York, New York; [†]Department of Cardiology, Homolka Hospital, Prague, Czech Republic; [‡]Division of Cardiology, St. John's Health Center, Santa Monica, California; [§]Division of Cardiology, Cedars Sinai Medical Center, Los Angeles, California; [‖]Division of Cardiology, Scripps Clinic, La Jolla, California; [¶]Division of Cardiology, Saint Luke's Mid America Heart Institute, Kansas City, Missouri; [#]Division of Cardiology, Texas Cardiac Arrhythmia Institute, Austin, Texas; [**]Foundation for Cardiovascular Medicine, La Jolla, California; [††]Boston Scientific Inc., St. Paul, Minnesota; and the [‡‡]Cardiovascular Medicine Department, Mayo Clinic, Rochester, Minnesota. The PREVAIL and PROTECT AF

- ✓ 1114 patients and 4343 patient years
- ✓ Composite endpoints were similar in the two groups
- ✓ 80% decrease in hemorrhagic stroke
- ✓ 59% decrease in disabling stroke
- ✓ 52% decrease in post-procedure bleeding
- ✓ 41% decrease in cardiovascular death
- ✓ 27% decrease in all-cause death
- ✓ SE and ischemic stroke were numerically higher in the device arm, but this did not reach statistical significance

5-Year Outcomes After Left Atrial Appendage Closure

From the PREVAIL and PROTECT AF Trials

Vivek Y. Reddy, MD,[a,b] Shephal K. Doshi, MD,[c] Saibal Kar, MD,[d] Douglas N. Gibson, MD,[e] Matthew J. Price, MD,[e] Kenneth Huber, MD,[f] Rodney P. Horton, MD,[g] Maurice Buchbinder, MD,[h] Petr Neuzil, MD, PhD,[b] Nicole T. Gordon, BSEE,[i] David R. Holmes, Jr, MD,[j] on behalf of the PREVAIL and PROTECT AF Investigators

ABSTRACT

BACKGROUND The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) trial demonstrated that left atrial appendage closure (LAAC) with the Watchman device (Boston Scientific, St. Paul, Minnesota) was equivalent to warfarin for preventing stroke in atrial fibrillation, but had a high rate of complications. In a second randomized trial, PREVAIL (Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy), the complication rate was low. The warfarin cohort experienced an unexpectedly low ischemic stroke rate, rendering the efficacy endpoints inconclusive. However, these outcomes were based on relatively few patients followed for a relatively short time.

OBJECTIVES The final results of the PREVAIL trial, both alone and as part of a patient-level meta-analysis with the PROTECT AF trial, are reported with patients in both trials followed for 5 years.

METHODS PREVAIL and PROTECT AF are prospective randomized clinical trials with patients randomized 2:1 to LAAC or warfarin; together, they enrolled 1,114 patients for 4,343 patient-years. Analyses are by intention-to-treat, and rates are events per 100 patient-years.

RESULTS For the PREVAIL trial, the first composite coprimary endpoint of stroke, systemic embolism (SE), or cardiovascular/unexplained death did not achieve noninferiority (posterior probability for noninferiority = 88.4%), whereas the second coprimary endpoint of post-procedure ischemic stroke/SE did achieve noninferiority (posterior probability for noninferiority = 97.5%); the warfarin arm maintained an unusually low ischemic stroke rate (0.77%). In the meta-analysis, the composite endpoint was similar between groups (hazard ratio [HR]: 0.820, p = 0.27), as were all-stroke/SE (HR: 0.961, p = 0.87). The ischemic stroke/SE rate was numerically higher with LAAC, but this difference did not reach statistical significance (HR: 1.71; p = 0.0803). However, differences in hemorrhagic stroke, disabling/fatal stroke, cardiovascular/unexplained death, all-cause death, and post-procedure bleeding favored LAAC (HR: 0.30; p = 0.0032; HR: 0.45; p = 0.03; HR: 0.59; p = 0.037; HR: 0.73; p = 0.035; HR: 0.48; p = 0.0003; respectively).

CONCLUSIONS These 5-year outcomes of the PREVAIL trial, combined with the 5-year outcomes of the PROTECT AF trial, demonstrate that LAAC with Watchman provides stroke prevention in nonvalvular atrial fibrillation comparable to warfarin, with additional reductions in major bleeding, particularly hemorrhagic stroke, and mortality. (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation; NCT00129545; and Evaluation of the WATCHMAN LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy; NCT00832442) (J Am Coll Cardiol 2017;70:2964–75) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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- ✓ **SE and ischemic stroke were numerically higher in the device arm, but this did not reach statistical significance**
- ✓ **The reduction in disabling stroke speaks to the differential functional impact of ischemic vs. hemorrhagic strokes**

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Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation

A Patient-Level Meta-Analysis

David R. Holmes, Jr, MD,* Shephal K. Doshi, MD,† Saibal Kar, MD,† Matthew J. Price, MD,§ Jose M. Sanchez, MD,‖ Horst Sievert, MD,¶ Miguel Valderrabano, MD,# Vivek Y. Reddy, MD**

ABSTRACT

BACKGROUND The risk-benefit ratio of left atrial appendage closure (LAAC) versus systemic therapy (warfarin) for prevention of stroke, systemic embolism, and cardiovascular death in nonvalvular atrial fibrillation (NVAF) requires continued evaluation.

OBJECTIVES This study sought to assess composite data regarding left atrial appendage closure (LAAC) in 2 randomized trials compared to warfarin for prevention of stroke, systemic embolism, and cardiovascular death in patients with nonvalvular AF.

METHODS Our meta-analysis included 2,406 patients with 5,931 patient-years (PY) of follow-up from the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) and PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trials, and their respective registries (Continued Access to PROTECT AF registry and Continued Access to PREVAIL registry).

RESULTS With mean follow-up of 2.69 years, patients receiving LAAC with the Watchman device had significantly fewer hemorrhagic strokes (0.15 vs. 0.96 events/100 patient-years [PY]; hazard ratio [HR]: 0.22; p = 0.004), cardiovascular/unexplained death (1.1 vs. 2.3 events/100 PY; HR: 0.48; p = 0.006), and nonprocedural bleeding (6.0% vs. 11.3%; HR: 0.51; p = 0.006) compared with warfarin. All-cause stroke or systemic embolism was similar between both strategies (1.75 vs. 1.87 events/100 PY; HR: 1.02; 95% CI: 0.62 to 1.7; p = 0.94). There were more ischemic strokes in the device group (1.6 vs. 0.9 and 0.2 vs. 1.0 events/100 PY; HR: 1.95 and 0.22, respectively; p = 0.05 and 0.004, respectively). Both trials and registries identified similar event rates and consistent device effect in multiple subsets.

CONCLUSIONS In patients with NVAF at increased risk for stroke or bleeding who are candidates for chronic anticoagulation, LAAC resulted in improved rates of hemorrhagic stroke, cardiovascular/unexplained death, and nonprocedural bleeding compared to warfarin. (J Am Coll Cardiol 2015;65:2614–23) © 2015 by the American College of Cardiology

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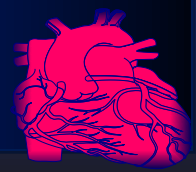
- ✓ **Meta-analysis of Protect AF, Prevail, and the CAP/CAP2 registries**
- ✓ **2406 patients ad 5391 patient years of follow-up**
- ✓ **Rates of hemorrhagic stroke, non-procedural bleeding, and c/v death were reduced in patients who received the LAA closure compared to long-term anticoagulation**



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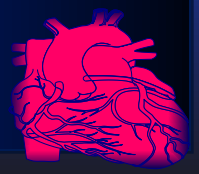
CONCLUSIONS In patients with NVAF at increased risk for stroke or bleeding who are candidates for chronic anticoagulation, LAAC resulted in improved rates of hemorrhagic stroke, cardiovascular/unexplained death, and nonprocedural bleeding compared to warfarin. (J Am Coll Cardiol 2015;65:2614-23) © 2015 by the American College of Cardiology

- ✓ **There is an increased risk of ischemic stroke even after exclusion of strokes in the first 7 days post procedure**
- ✓ **Likely due to the fact that not all strokes arise from the LAA**
- ✓ **Rates of hemorrhagic stroke, non-procedural bleeding, and c/v death were reduced in patients who received the LAA closure compared to long-term anticoagulation**



2019 AHA/ACC/HRS Focused Update of the 2014 Guideline for Management of Patients with Atrial Fibrillation

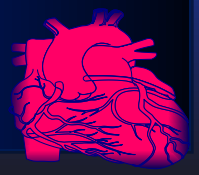
A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society

Recommendation for Percutaneous Approaches to Occlude the LAA

COR	LOE	Recommendation
IIb	B-NR	1. Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation. **NEW**: Clinical trial data and FDA approval of the Watchman device necessitated this recommendation.

Recommendation for Cardiac Surgery—LAA Occlusion/Excision

COR	LOE	Recommendation
IIb	B-NR	1. Surgical occlusion of the LAA may be considered in patients with AF undergoing cardiac surgery, as a component of an overall heart team approach to the management of AF. **MODIFIED**: LOE was updated from C to B-NR because of new evidence.



Future Questions

- No trials to date to compare LAA vs. no therapy in patients with contraindication to any antiplatelet or anticoagulation
- Some data suggest that Watchman vs. DAPT is favorable in patients who have contraindications to anticoagulation
- No significant data available regarding NOACs vs. Watchman (although small patient numbers suggest it is similar to Coumadin data

Borgess Heart Center of Excellence

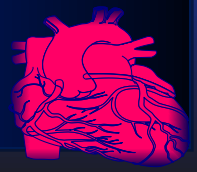
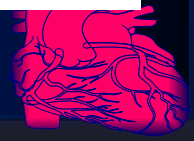


TABLE 4 5-Year Patient-Level Meta-Analysis of PROTECT AF and PREVAIL (2:1 Randomization)

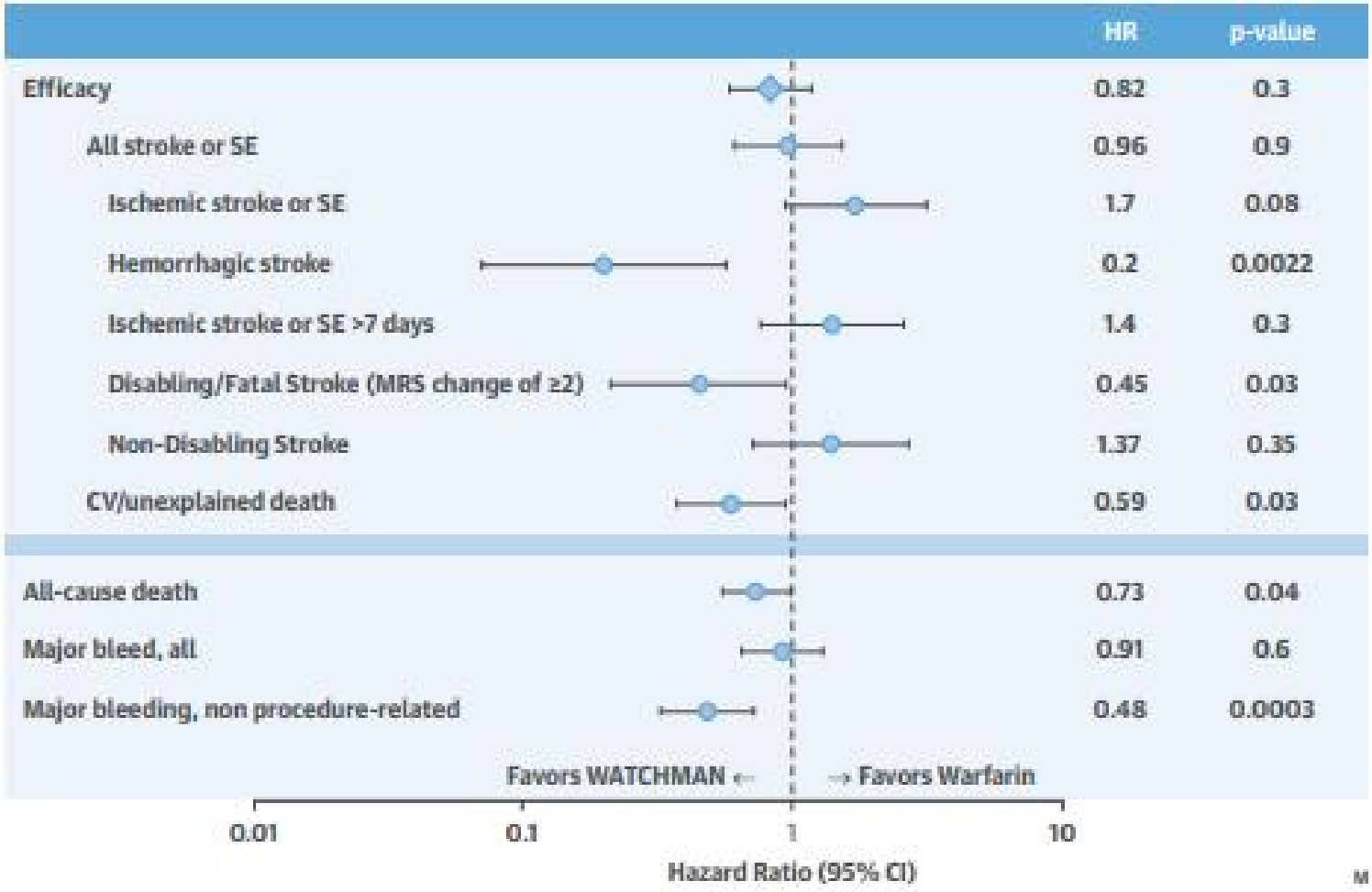
	Device Group (n = 732)		Control Group (n = 382)			
	No. of Events	Rate (per 100 PY)	No. of Events	Rate (per 100 PY)	Hazard Ratio (95% Confidence Interval)	p Value
Efficacy: stroke/SE/CV death	79/2,856.0	2.8%	50/1,472.8	3.4%	0.82 (0.58-1.17)	0.27
All stroke or SE	49/2,849.4	1.7%	27/1,472.9	1.8%	0.96 (0.60-1.54)	0.87
Ischemic stroke or SE	45/2,850.2	1.6%	14/1,479.1	0.95%	1.71 (0.94-3.11)	0.08
Hemorrhagic stroke	5/2,954.8	0.17%	13/1,499.0	0.87%	0.20 (0.07-0.56)	0.0022
Ischemic stroke or SE >7 days	37/2,862.1	1.3%	14/1,479.1	0.95%	1.40 (0.76-2.59)	0.28
Disabling stroke	13/2,943.0	0.44%	15/1,493.8	1.0%	0.45 (0.21-0.94)	0.03
Nondisabling stroke	31/2,879.1	1.1%	12/1,484.3	0.81%	1.38 (0.71-2.68)	0.35
CV/unexplained death	39/2,960.5	1.3%	33/1,505.2	2.2%	0.59 (0.37-0.94)	0.027
All-cause death	106/2,961.6	3.6%	73/1,505.2	4.9%	0.73 (0.54-0.98)	0.035
Major bleeding, all	85/2,748.4	3.1%	50/1,414.7	3.5%	0.91 (0.64-1.29)	0.60
Major bleeding, non-procedure-related	48/2,853.6	1.7%	51/1,411.3	3.6%	0.48 (0.32-0.71)	0.0003

Two strokes in PREVAIL are excluded because the baseline MRS score was unavailable. Disabling stroke is defined as a stroke that increases the Modified Rankin Score by ≥2.

PY = patient-yrs. Other abbreviations as in Table 3.



CENTRAL ILLUSTRATION Stroke Prevention in Nonvalvular Atrial Fibrillation With LAA Closure



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ORIGINAL RESEARCH ARTICLE

Device-Related Thrombus After Left Atrial Appendage Closure

Incidence, Predictors, and Outcomes

Editorial, see p 886

Srinivas R. Dukkipati, MD
Saibal Kar, MD
David R. Holmes, MD
Shephal K. Doshi, MD
Vijendra Swarup, MD
Douglas N. Gibson, MD
Brijeshwar Maini, MD
Nicole T. Gordon, BSEE
Michael L. Main, MD
Vivek Y. Reddy, MD

BACKGROUND: In patients with atrial fibrillation, left atrial appendage closure with the Watchman device prevents thromboembolism from the left atrial appendage; however, thrombus may form on the left atrial face of the device, and then potentially embolize. Herein, we studied the incidence, predictors, and clinical outcome of device-related thrombus (DRT) using a large series of clinical trial cohorts of patients undergoing Watchman implantation.

METHODS: We studied the device arms of 4 prospective Food and Drug Administration trials: PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) (n=463); PREVAIL (Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) (n=269); CAP (Continued Access to PROTECT AF registry) (n=566); and CAP2 (Continued Access to PREVAIL registry) (n=578). Surveillance transesophageal echocardiographs were performed at 45 days and 12 months in all patients, and also at 6 months in the randomized control trials. We assessed both the incidence of DRT during these transesophageal echocardiographs (and other unscheduled transesophageal echocardiographs), and clinical outcomes of postprocedure stroke or systemic embolism (SSE) and adjusted for CHA_2DS_2-VASC and HAS-BLED scores.

RESULTS: Of 1739 patients who received an implant (7159 patient-years follow-up; CHA_2DS_2-VASc=4.0), DRT was seen in 65 patients (3.74%). The rates of SSE with and without DRT were 7.46 and 1.78 per 100 patient-years (adjusted rate ratio, 3.55; 95% confidence interval [CI], 2.18–5.79; P<0.001), and ischemic SSE rates were 6.28 and 1.65 per 100 patient-years (adjusted rate ratio, 3.22; 95% CI, 1.90–5.45, P<0.001). On multivariable modeling analysis, the predictors of DRT were as follows: history of transient ischemic attack or stroke (odds ratio [OR], 2.31; 95% CI, 1.26–4.25; P=0.007), permanent atrial fibrillation (OR, 2.24; 95% CI, 1.19–4.20; P=0.012); vascular disease (OR, 2.06; 95% CI, 1.08–3.91; P=0.028); left atrial appendage diameter (OR, 1.06 per mm increase; 95% CI, 1.01–1.12; P=0.019); left ventricular ejection fraction (OR, 0.96 per 1% increase; 95% CI, 0.94–0.99; P=0.009). DRT and SSE both occurred in 17 of 65 patients (26.2%). Of the 19 SSE events in these patients with DRT, 9 of 19 (47.4%) and 12 of 19 (63.2%) occurred within 1 and 6 months of DRT detection. Conversely, after left atrial appendage closure, most SSEs (123/142, 86.62%) occurred in patients without DRT.

CONCLUSIONS: After left atrial appendage closure with Watchman, DRT (≈3.7%) is not frequent but, when present, is associated with a higher rate of stroke and systemic embolism.

Key Words: atrial appendage ■ atrial fibrillation ■ percutaneous coronary intervention ■ stroke ■ thrombosis

Sources of Funding, see page 886

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Circulation. 2018;138:874–885. DOI: 10.1161/CIRCULATIONAHA.118.035090

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- ✓ 1739 patients from the Protect AF / Prevail / CAP / CAP2
- ✓ Data based on 45 day, 6 month, and 1 year TEE studies
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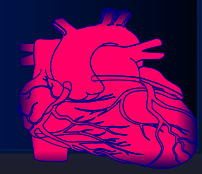

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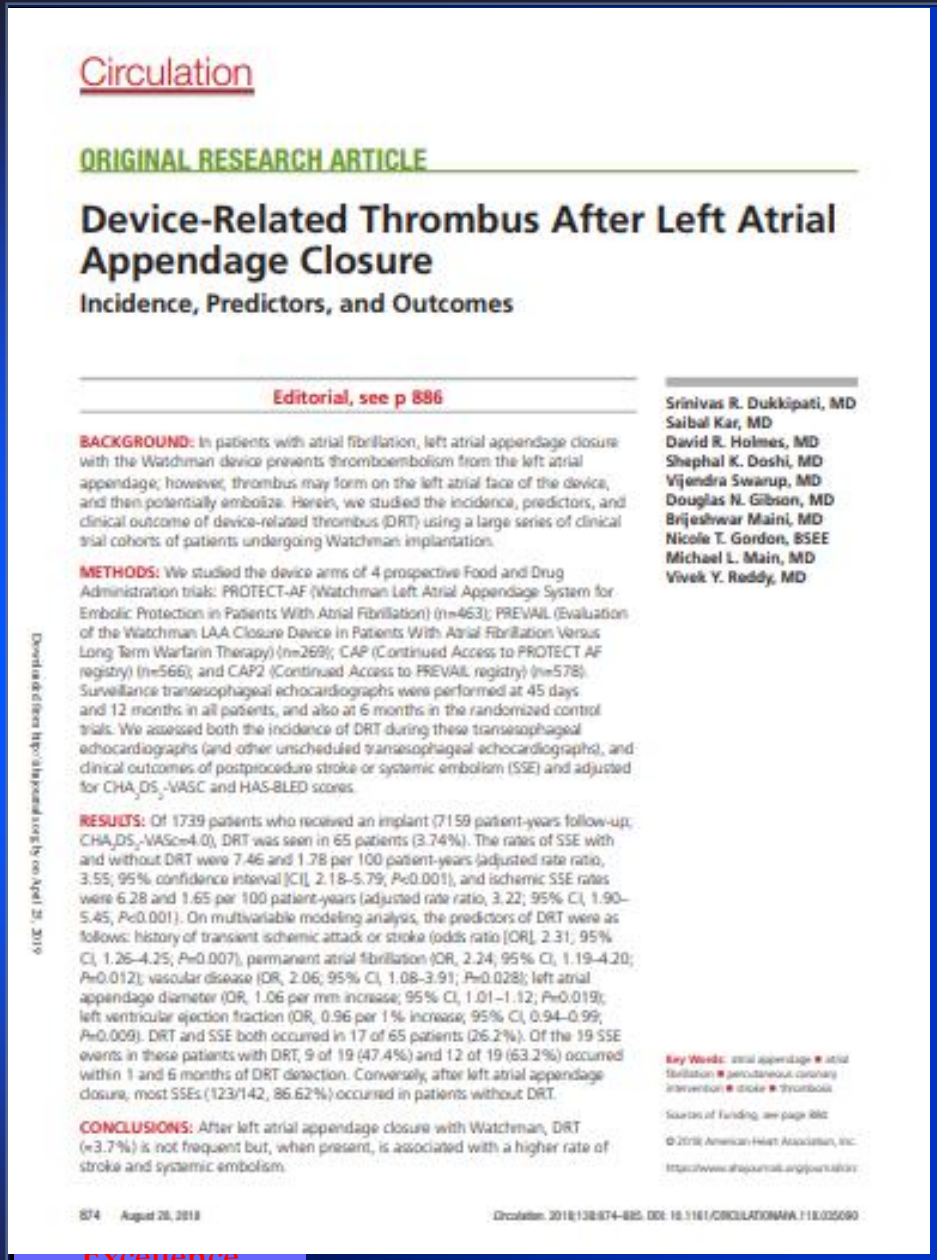
- ✓ **The majority of DRT found at 6 and 12 month TEE studies – which was after Warfarin discontinued**
- ✓ **25% (16/65) of those with DRT had an ischemic stroke or SE**
- ✓ **6.8% in those without DRT**



Circulation

ORIGINAL RESEARCH ARTICLE

Device-Related Thrombus After Left Atrial Appendage Closure

Incidence, Predictors, and Outcomes

Editorial, see p 886

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BACKGROUND: In patients with atrial fibrillation, left atrial appendage closure with the Watchman device prevents thromboembolism from the left atrial appendage; however, thrombus may form on the left atrial face of the device, and then potentially embolize. Herein, we studied the incidence, predictors, and clinical outcome of device-related thrombus (DRT) using a large series of clinical trial cohorts of patients undergoing Watchman implantation.

METHODS: We studied the device arms of 4 prospective Food and Drug Administration trials: PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) (n=463); PREVAIL (Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) (n=269); CAP (Continued Access to PROTECT AF registry) (n=566); and CAP2 (Continued Access to PREVAIL registry) (n=578). Surveillance transesophageal echocardiographs were performed at 45 days and 12 months in all patients, and also at 6 months in the randomized control trials. We assessed both the incidence of DRT during these transesophageal echocardiographs (and other unscheduled transesophageal echocardiographs), and clinical outcomes of postprocedure stroke or systemic embolism (SSE) and adjusted for CHA_2DS_2-VASC and HAS-BLED scores.

RESULTS: Of 1739 patients who received an implant (7159 patient-years follow-up; CHA_2DS_2-VASc=4.0), DRT was seen in 65 patients (3.74%). The rates of SSE with and without DRT were 7.46 and 1.78 per 100 patient-years (adjusted rate ratio, 3.55; 95% confidence interval [CI], 2.18–5.79; $P<0.001$), and ischemic SSE rates were 6.28 and 1.65 per 100 patient-years (adjusted rate ratio, 3.22; 95% CI, 1.90–5.45; $P<0.001$). On multivariable modeling analysis, the predictors of DRT were as follows: history of transient ischemic attack or stroke (odds ratio [OR], 2.31; 95% CI, 1.26–4.25; $P=0.007$), permanent atrial fibrillation (OR, 2.24; 95% CI, 1.19–4.20; $P=0.012$), vascular disease (OR, 2.06; 95% CI, 1.08–3.91; $P=0.028$); left atrial appendage diameter (OR, 1.06 per mm increase; 95% CI, 1.01–1.12; $P=0.019$); left ventricular ejection fraction (OR, 0.96 per 1% increase; 95% CI, 0.94–0.99; $P=0.009$). DRT and SSE both occurred in 17 of 65 patients (26.2%). Of the 19 SSE events in these patients with DRT, 9 of 19 (47.4%) and 12 of 19 (63.2%) occurred within 1 and 6 months of DRT detection. Conversely, after left atrial appendage closure, most SSEs (123/142, 86.62%) occurred in patients without DRT.

CONCLUSIONS: After left atrial appendage closure with Watchman, DRT (≈3.7%) is not frequent but, when present, is associated with a higher rate of stroke and systemic embolism.

Key Words: atrial appendage ● atrial fibrillation ● percutaneous coronary intervention ● stroke ● thrombosis

Sources of Funding, see page 886

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- ✓ **Things we don't know:**
  - **(a) What was the characteristics of the DRT**
  - **(b) How the patients with DRT were treated and anticoagulated post recognition**
- ✓ **Individual factors associated with DRT:**
  - **(a) Permanent AF**
  - **(b) Increasing Chads-vasc Score**
  - **(c) Larger LAA diameter**
  - **(d) Lower LAA emptying velocity**
  - **(e) Presence of Heart Failure**

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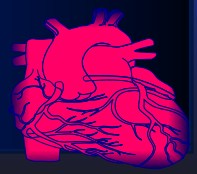
- ✓ **What is the best post-procedure regimen to reduce DRT?**
  - **(a) Anticoag to 3 – 6 months**
  - **(b) Longer term low-dose NOAC**
  - **(c) DAPT indefinitely**
  - **(d) ASAP trial(s)**
- ✓ **Should we be doing routine TEE post device implantation to assess for DRT?**



Contraindications

- Intracardiac thrombus is visualized by echocardiographic imaging.
- An atrial septal defect repair / closure device or a PFO repair / closure device is present.
- The LAA anatomy will not accommodate a device.
- Any of the customary contraindications for other percutaneous catheterization procedures:
  - Catheter sizes, active infection, bleeding disorder
- There are contraindications to the use of warfarin, aspirin, or clopidogrel**
- The patient has a known hypersensitivity to any portion of the device material or the individual components (nitinol: nickel and titanium)

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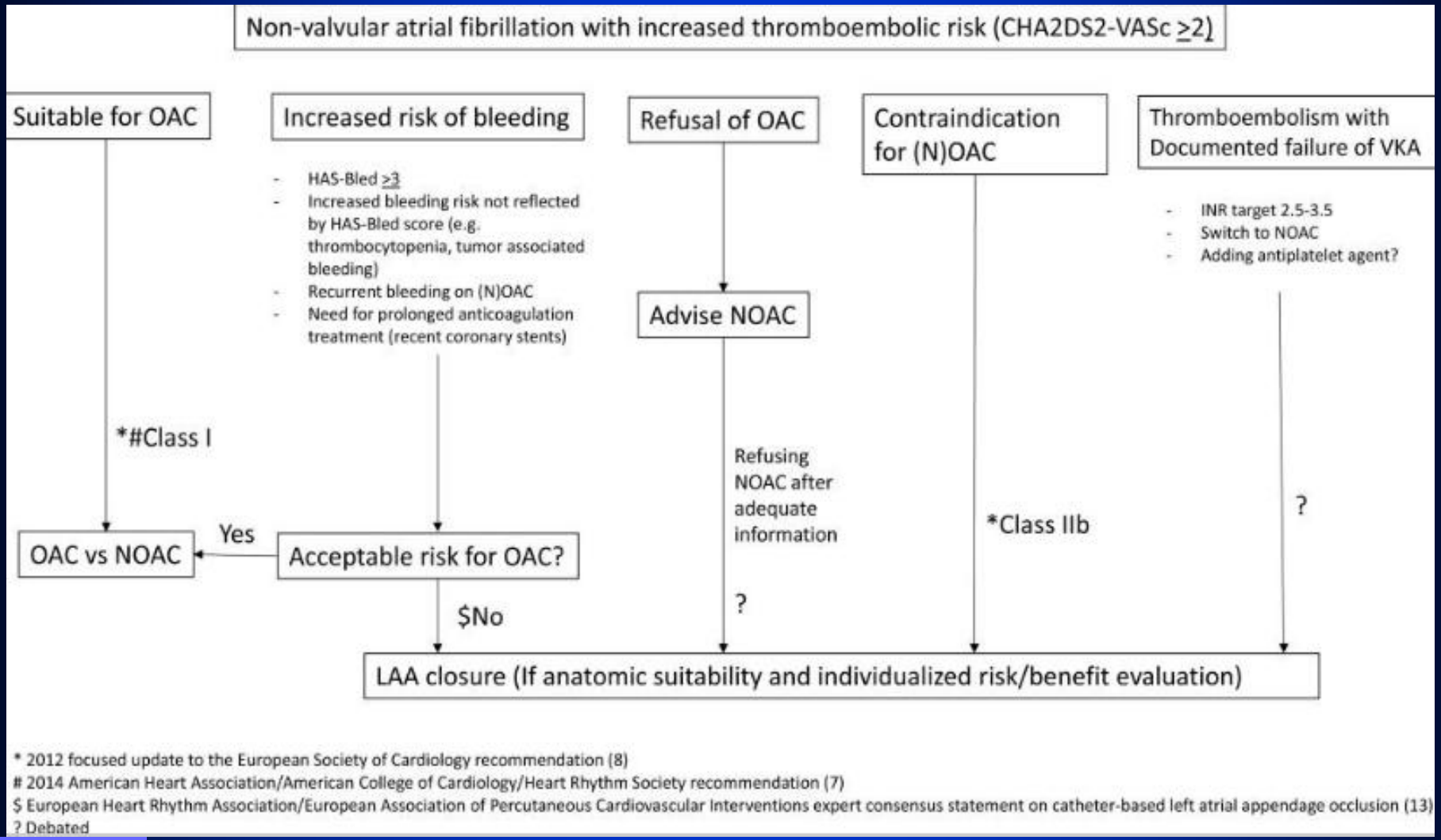

* 2012 focused update to the European Society of Cardiology recommendation (8)
# 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society recommendation (7)
$ European Heart Rhythm Association/European Association of Percutaneous Cardiovascular Interventions expert consensus statement on catheter-based left atrial appendage occlusion (13)
? Debated

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The Devices

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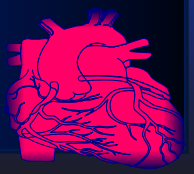

PLAATO DEVICE

First percutaneous LAA occlusion device(1998)

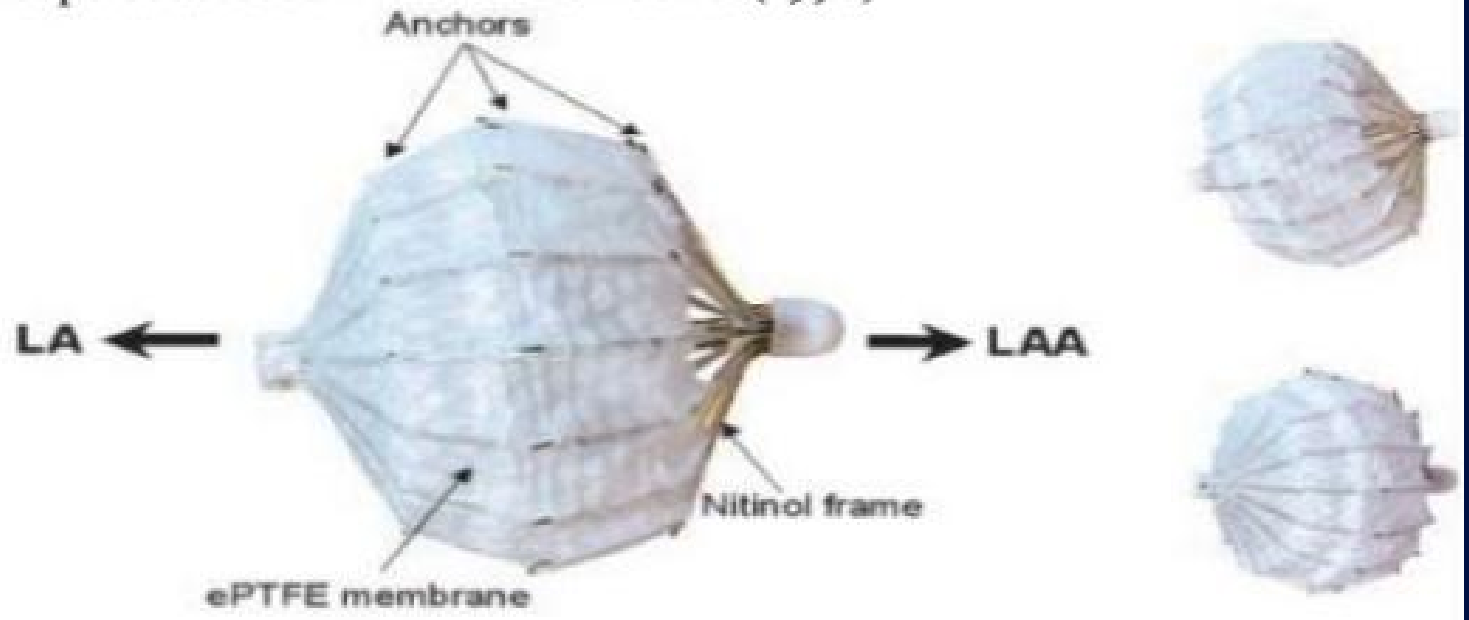

Figure 1. The implant is constructed of a nitinol frame and an implant occlusion membrane consisting of a laminated ePTFE. Small anchors along the frame and passing through the occlusive membrane assist with device anchoring.

Endocardial LAAO Devices

- Watchman (Boston Scientific):
  - Only device studied in randomized devices to date
  - CE Approval in 2005
  - FDA approval in 2015

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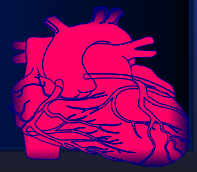

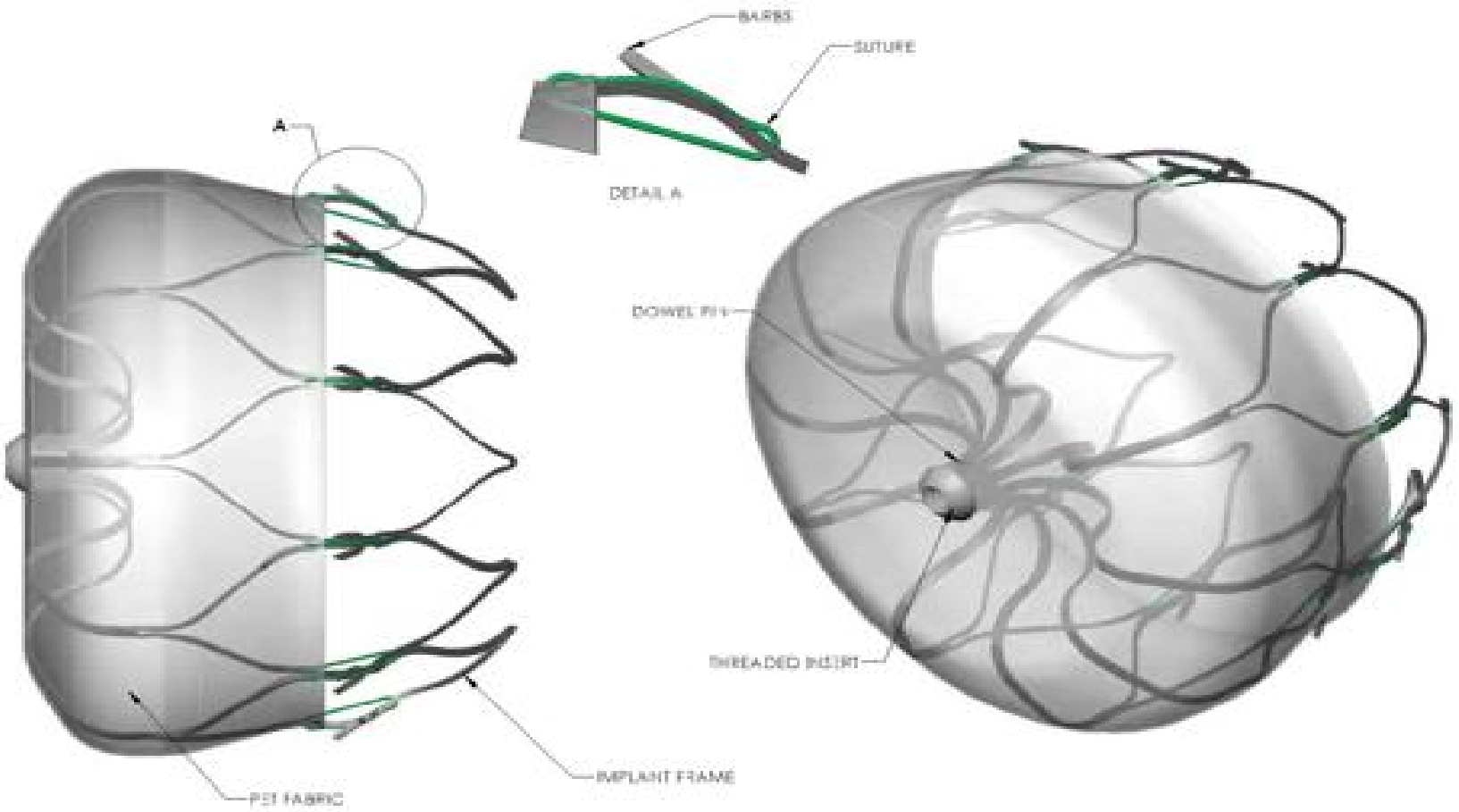

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Watchman Device

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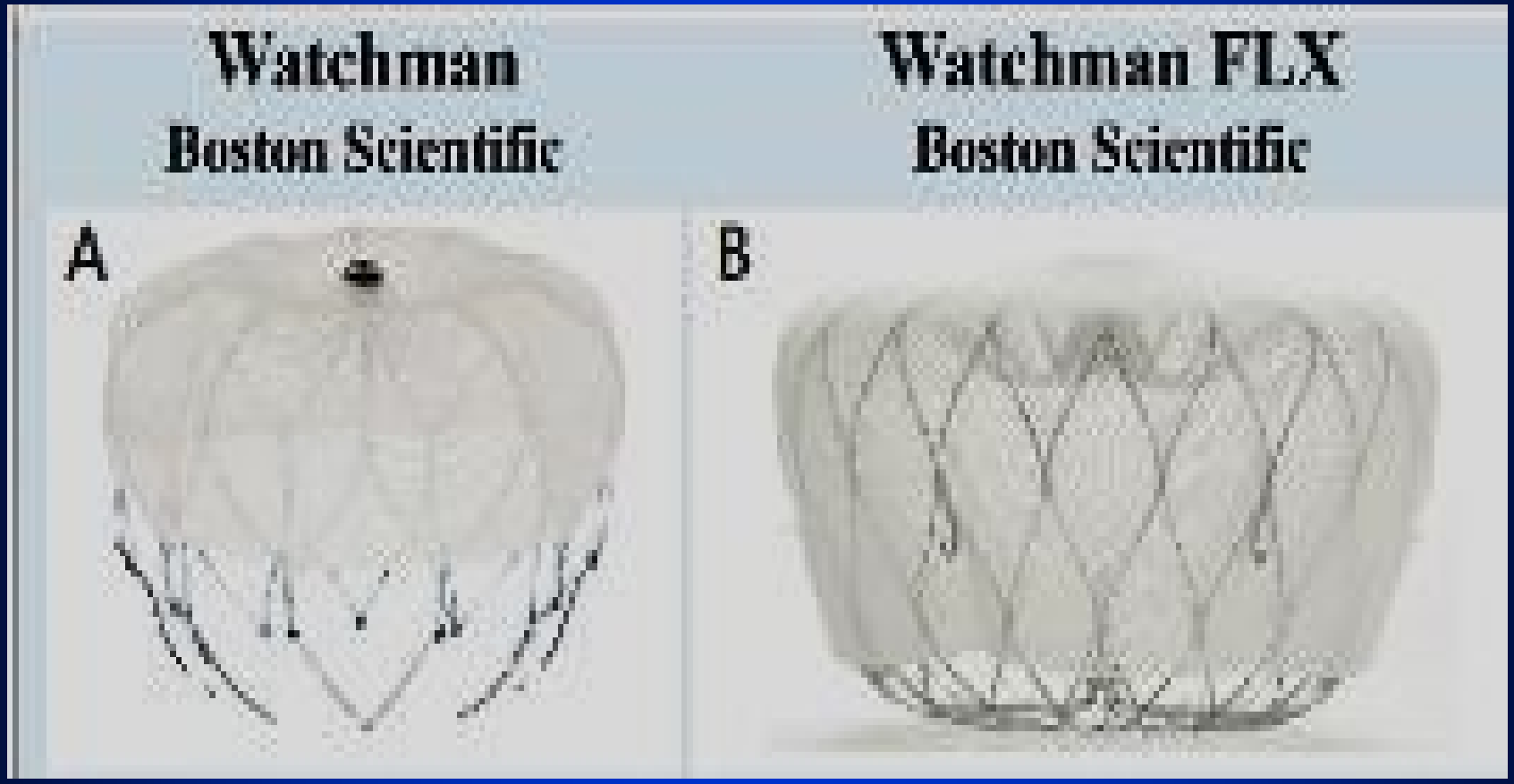

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DEVICE RELEASE CRITERIA

All criteria must be met prior to device release *(PASS)*

Position – device is distal to or at the ostium of the LAA

Anchor – fixation anchors engaged / device is stable

Size – device is compressed 8-20% of original size

Seal – device spans ostium, all lobes of LAA are covered

– If necessary, device can be recaptured (partial or full)

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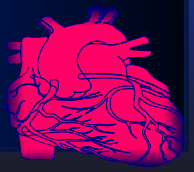

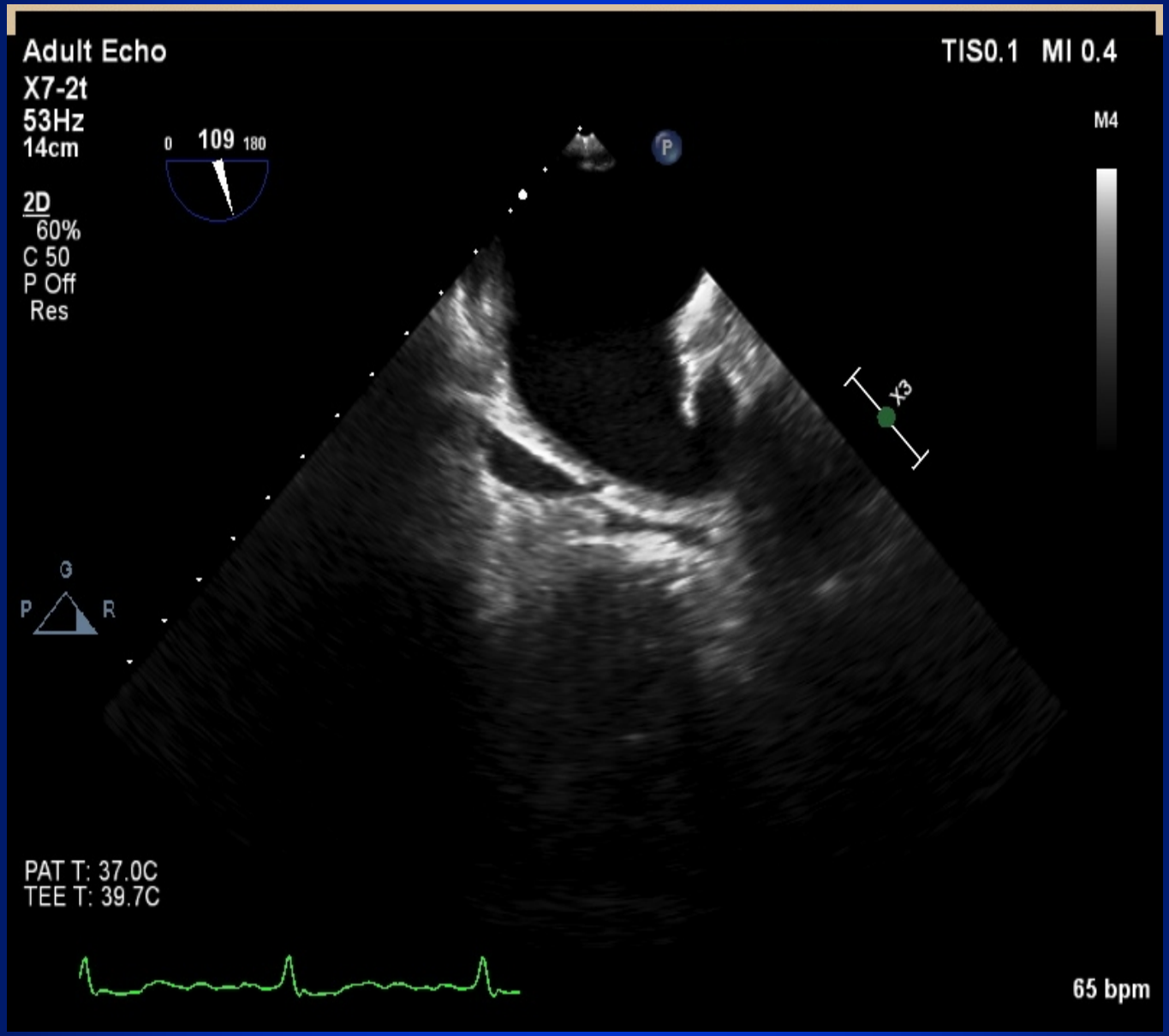

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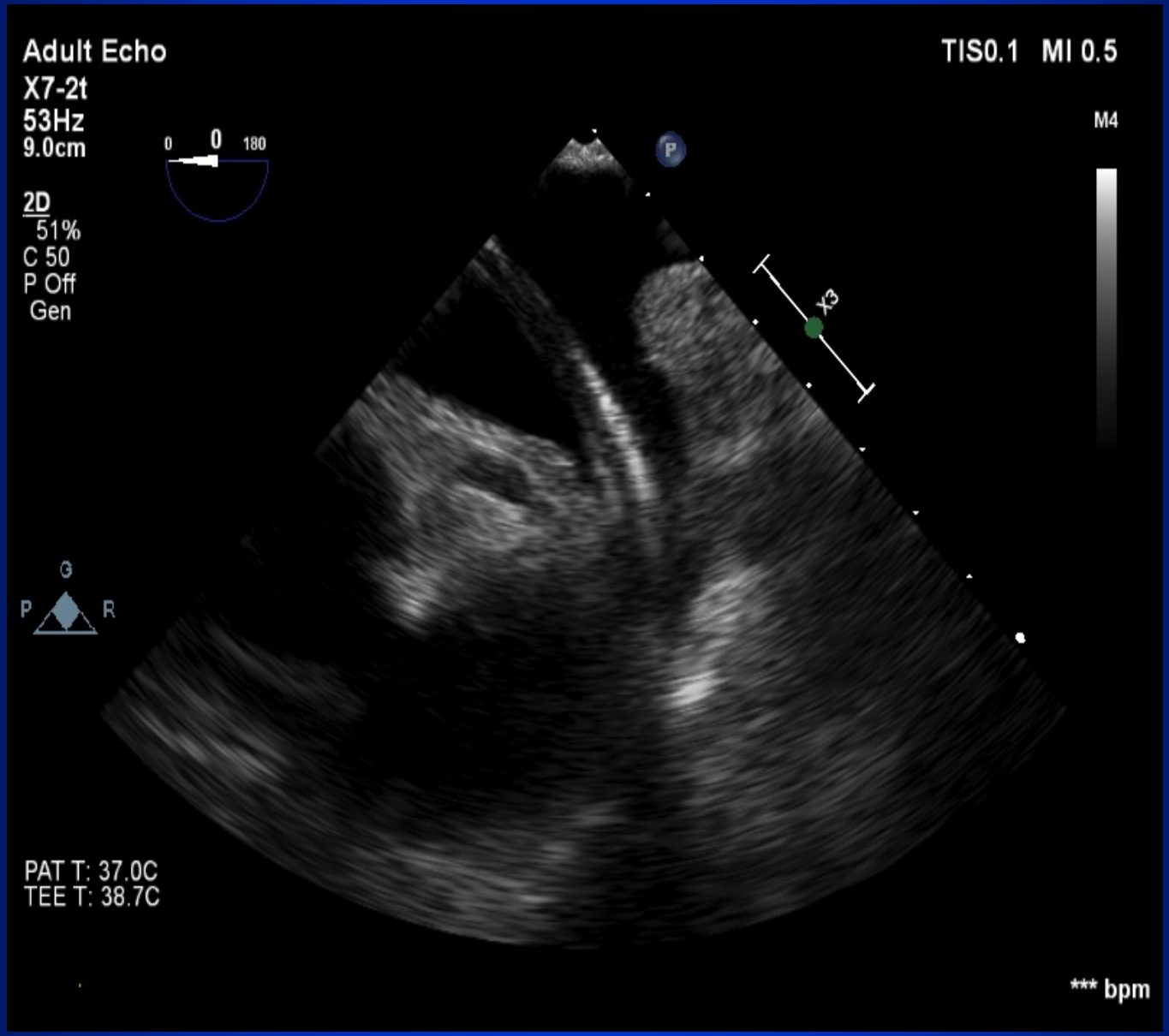

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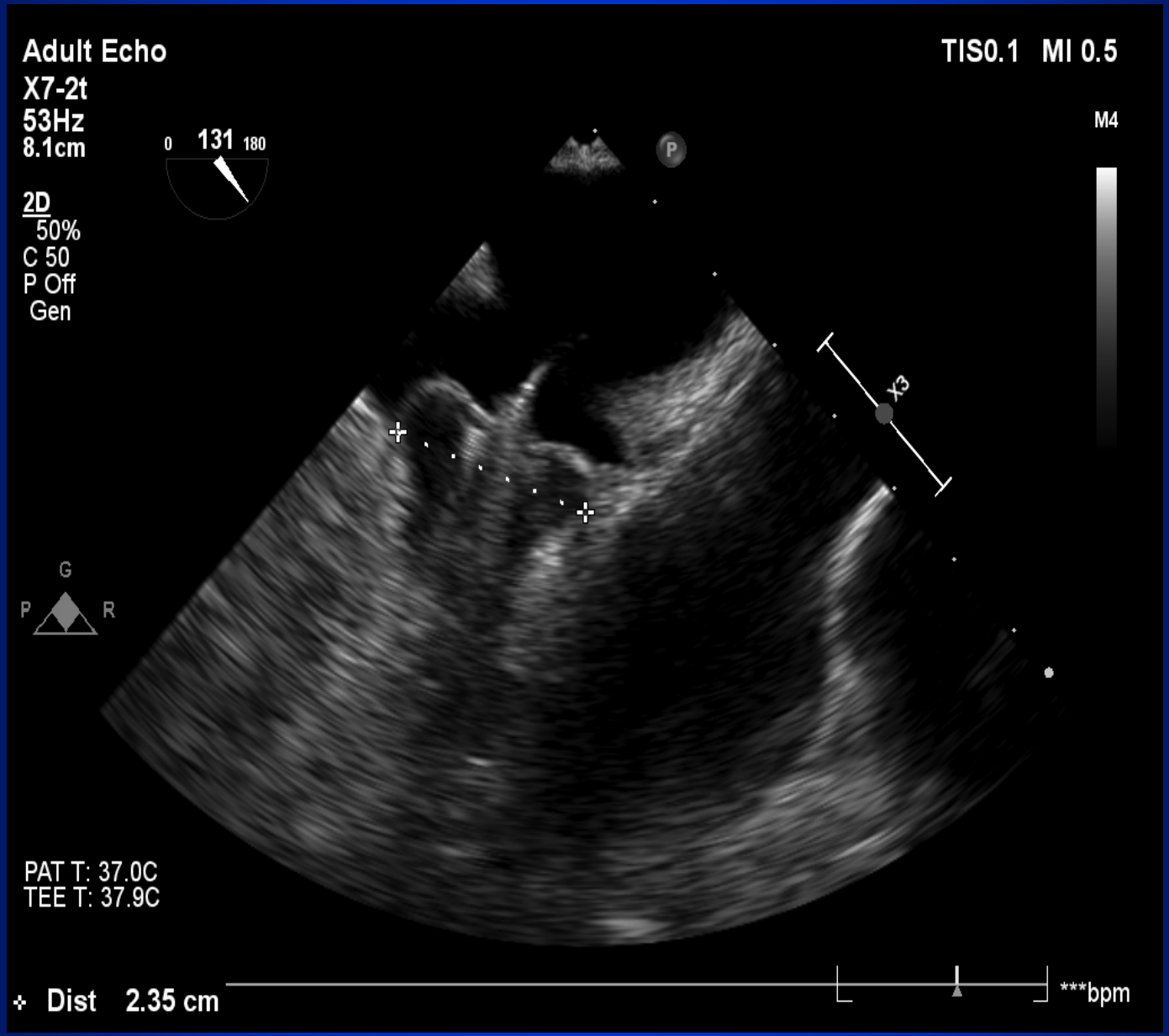

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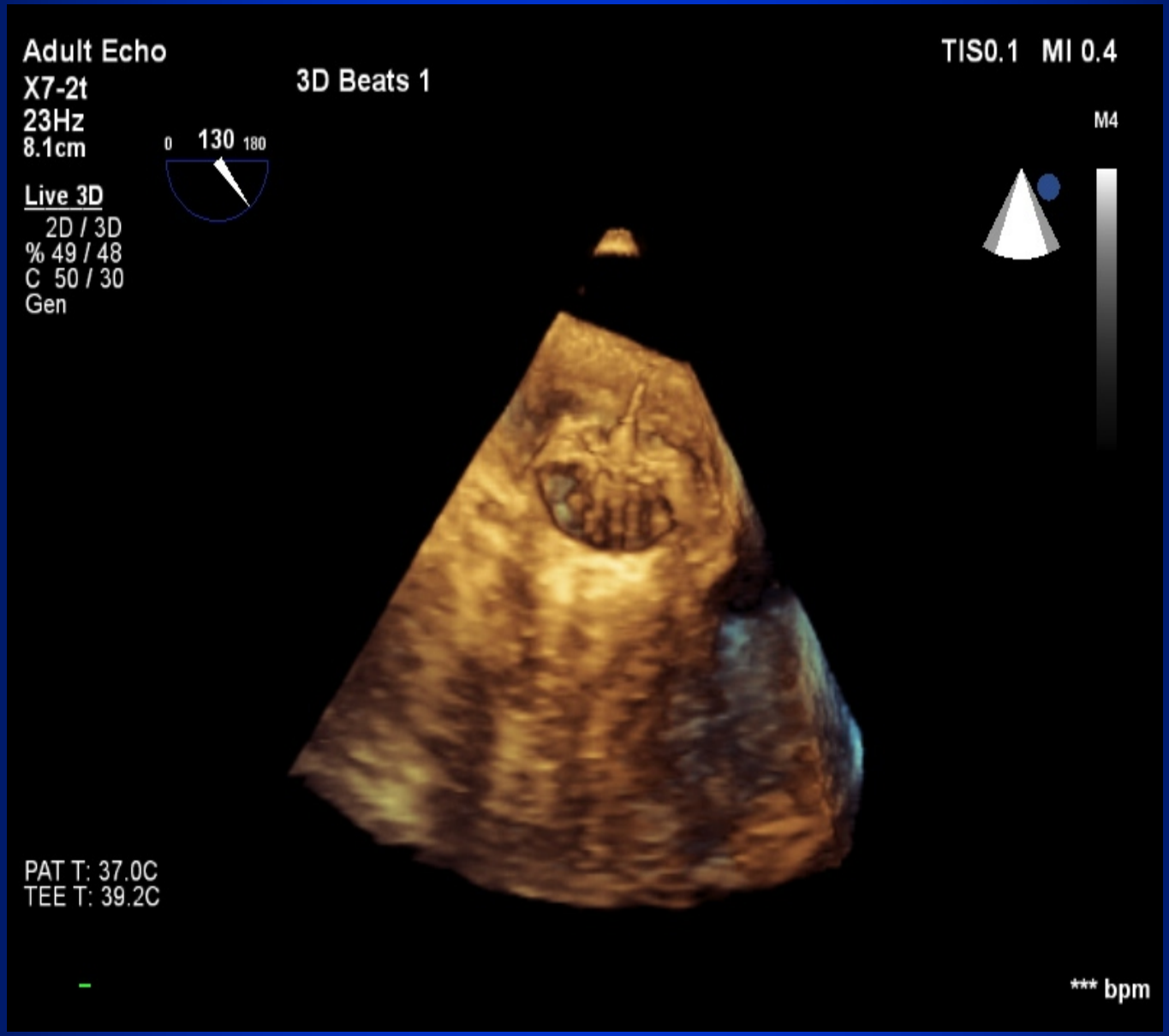

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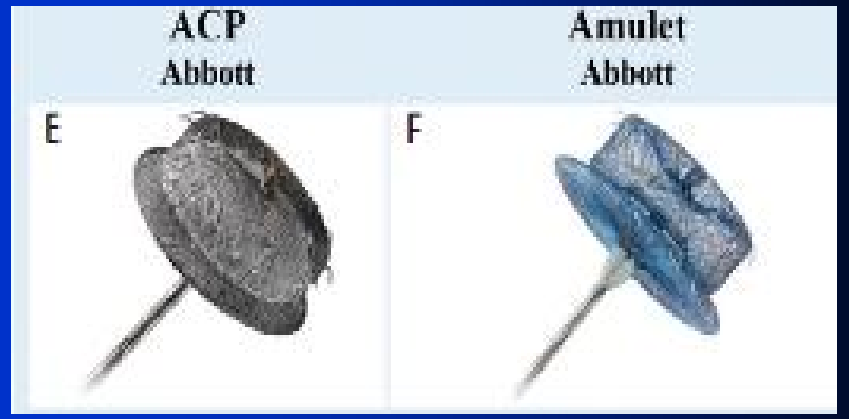
Endocardial LAAO Devices

- Amplatzer Cardiac Plug and Amplatzer Amulet Device (Abbott Vascular):
  - Ongoing Amulet investigational device exemption (IDE) trial will randomize > 1800 patients in a 1:1 fashion to either Amulet or Watchman with a 5 year follow-up
  - CE Mark for ACP 2008
  - CE Mark for Amulet 2013



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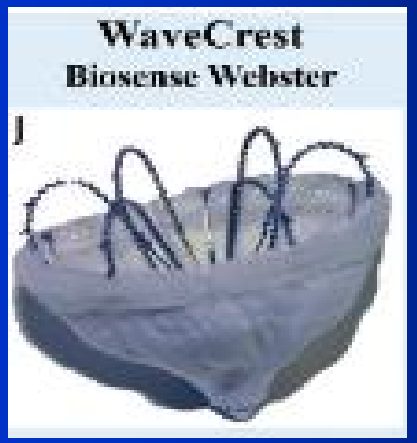
Endocardial LAAO Devices

- **Wavecrest LAAO system Biosense Webster / J&J:**
  - **CE Mark 2013**



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Endocardial LAAO Devices

- **Occlutech LAA Occluder (Occlutech International AB):**
  - **CE Mark 2016**
    - ***Withdrawn shortly after due to device embolization***
    - ***Newer device trial is underway***

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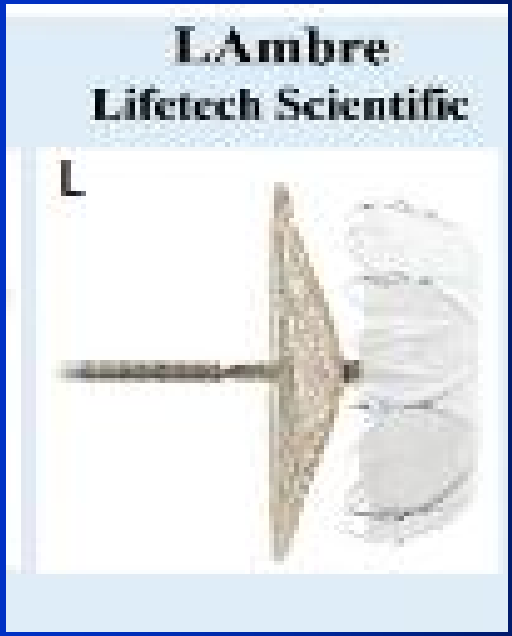
Endocardial LAAO Devices

- Lambre LAA Closure System (Lifetech Scientific Co):
  - Received CE Mark in 2016



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Endocardial LAAO Devices

- Sideris Patch and Prolipsis Custom Medical Devices):
  - Frameless, bioabsorbable device
  - Still investigational

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Endocardial LAAO Devices

- Ultraseal: (Cardia)
  - CE Mark in 2016

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Endocardial LAAO Devices

- **Pfm Device (Pfm Medical):**
  - Currently in pre-clinical trials

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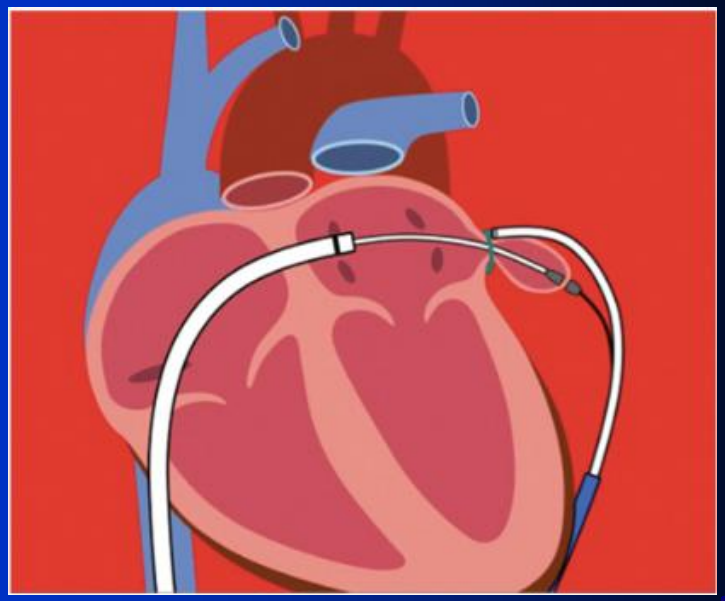
Epicardial LAAO Devices

- Lariet Device (SenntreHeart, Inc)
  - Epicardial and endocardial approach
  - CE Mark 2015
  - FDA Approval 2006 (not for LAAO)



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Epicardial LAAO Devices

- Sierra Ligation System (Aegi Medical Innovations)
  - ECG-guided LAA ligation via epicardial only approach
  - Feasibility Studies ongoing

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Surgical Excision

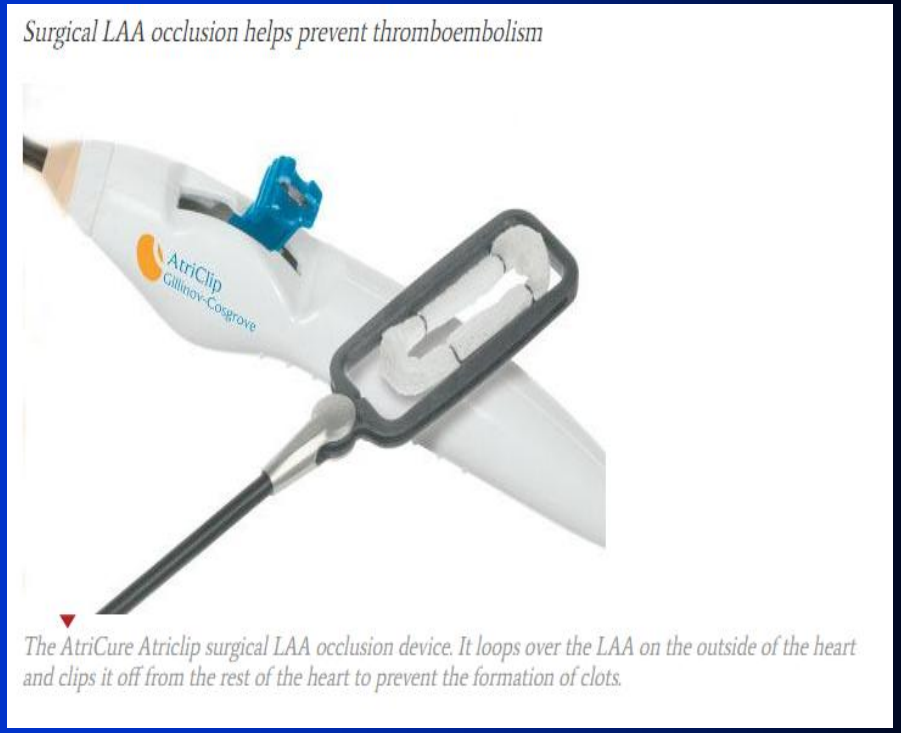

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TABLE 1. CURRENT DEVICES FOR PERCUTANEOUS LAAO

Device	Manufacturer	Design	Sizes (mm)	Sheath (F)	Approval Status
Endocardial LAAO Devices					
Watchman	Boston Scientific Corporation	Single (lobe)	21, 24, 27, 30, 33	14	CE Mark (2005); FDA (2015)
Watchman FLX			20, 24, 27, 31, 35	14	CE Mark (2015); withdrawn (2016)
Amplatzer Cardiac Plug	Abbott Vascular, formerly St. Jude Medical	Double (lobe and disc)	16, 18, 20, 22, 24, 26, 28, 30	9–13	CE Mark (2008)
Amplatzer Amulet			16, 18, 20, 22, 25, 28, 31, 34	12–14	CE Mark (2013)
WaveCrest	Biosense Webster, Inc., a Johnson & Johnson company	Single (lobe)	22, 27, 32	12	CE Mark (2013)
Occlutech	Occlutech International AB	Single (lobe)	15, 18, 21, 24, 27, 30, 33, 36, 39	12, 14	CE Mark (2016)
LAmbre	Lifetech Scientific Co., Ltd.	Double (umbrella and cover)	16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36	8–10	CE Mark (2016); CFDA (2017)
Sideris Transcatheter Patch	Custom Medical Devices	Frameless, bioabsorbable, balloon-deliverable device	15–25	13	Undergoing clinical evaluation
Ultraseal	Cardia, Inc.	Double (bulb and sail)	16, 18, 20, 22, 24, 26, 28, 30, 32	10–12	CE Mark (2016)
SeaLA	Hangzhou Valued Medtech Co., Ltd.	Double (dual disc)	16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36	9–12	Undergoing clinical evaluation
LeFort	Lepu Medical Technology (Beijing) Co., Ltd.	Single (lobe)	21–33	–	Undergoing clinical evaluation
Epicardial LAAO Devices					
Lariat	SentreHeart, Inc.	Endoepicardial	40 (W) (45 [W] Lariat +) X 20 (H) X 70 (L)	12	CE Mark (2015); FDA 510(k) (2006), surgical use only
Sierra	Aegis Medical Innovations Inc.	Epicardial	Single size	20	Undergoing clinical evaluation

Abbreviations: CFDA, China Food and Drug Administration; FDA, US Food and Drug Administration; H, height; L, length; LAAO, left atrial appendage occlusion; W, width.

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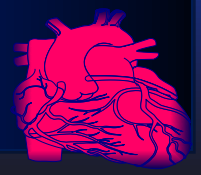

Important Future Trials

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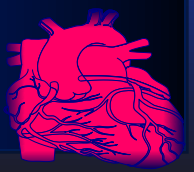

AMPLATZER™ Amulet™ LAA Occluder Trial (Amulet IDE)

Study Design

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	1878 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Prevention
Official Title:	AMPLATZER™ Amulet™ Left Atrial Appendage Occluder Randomized Controlled Trial
Study Start Date :	August 2016
Estimated Primary Completion Date :	February 2020
Estimated Study Completion Date :	December 2023

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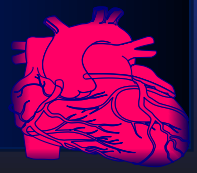

Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation (PRAGUE-17)

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	400 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Prevention
Official Title:	Interventional Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in High-risk Patients With Atrial Fibrillation (PRAGUE-17 Study)
Study Start Date :	April 2015
Estimated Primary Completion Date :	May 20, 2019
Estimated Study Completion Date :	May 2020

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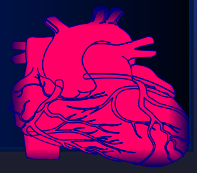

Watchman Practical Thoughts

- OAC (either Warfarin or a NOAC) is the mainstay of cardioembolic protection in patients with AF and an elevated CHA_2DS_2-VASc score
- > 90 of thrombi in AF arise from the LAA
- In patients that are unable to safely take OAC, occlusion of the LAA appears, according to available data to date, a reasonable alternative to OAC
  - Trials have been designed to be non-inferiority trials, not superiority trials
    - Meaning to say:
      - *Watchman device is not a better choice than OAC*

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