Left Atrial Appendage Closure for Stroke Prevention in Atrial Fibrillation

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Relevant Disclosures

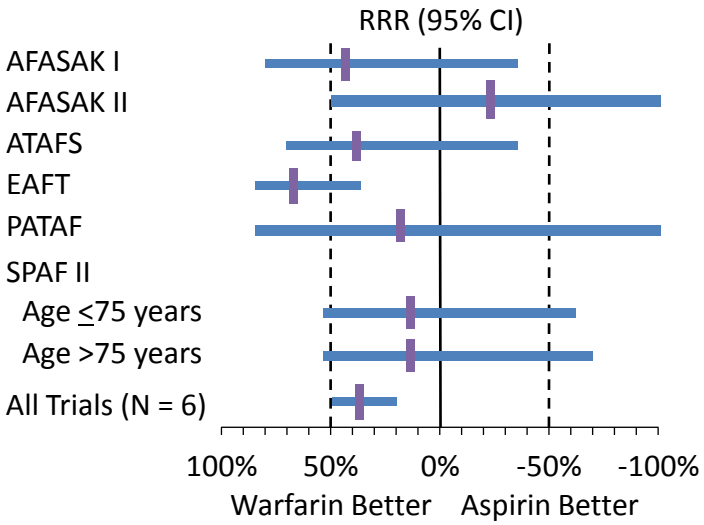
None

ACC/AHA 2014 Atrial Fibrillation Guideline Recommendations for Antithrombotic Therapy*

CHA_2DS_2–VASc Score	Recommended Therapy	Guideline Recommendation
0	No antithrombotic therapy	
1	Oral anticoagulant**, aspirin, or no antithrombotic therapy	
≥ 2	Oral anticoagulant** - With warfarin (IA) - With a NOAC (IB)	 

*The same antithrombotic recommendations apply to atrial flutter
**A direct thrombin or factor Xa inhibitor is recommended if there is inability to maintain a therapeutic INR (Class I, Level C)
January CT et al. JACC 2014;Epub

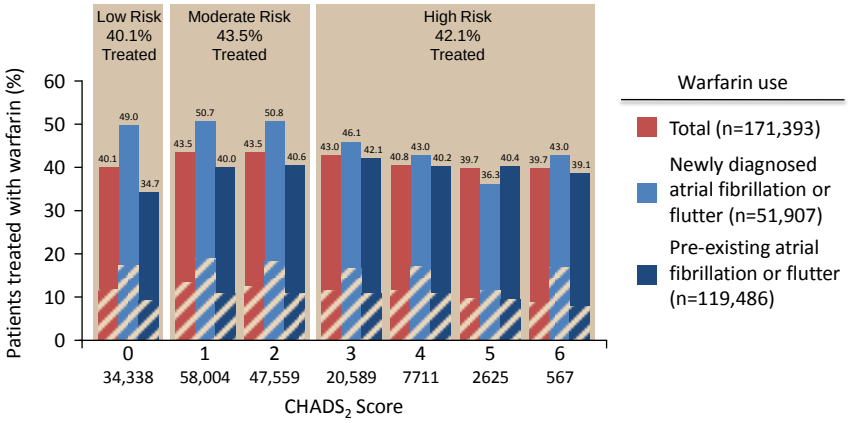
Efficacy of Warfarin (as Compared to Aspirin) in Stroke Prevention



RRR=Relative risk reduction
Hart RG et al. Ann Intern Med 1999;131:492-501

Warfarin Remains Vastly Underutilized

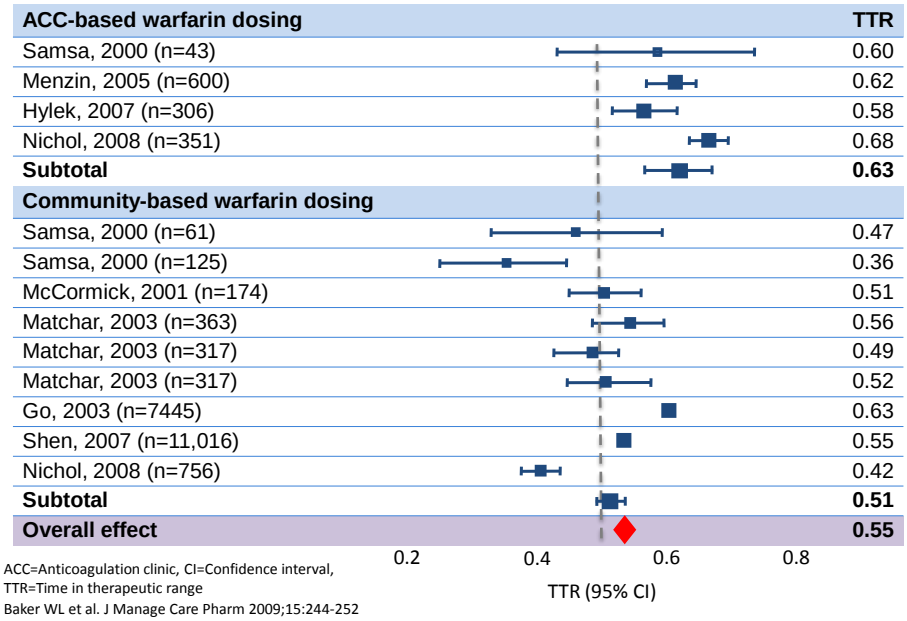
Retrospective cohort of 171,393 patients with atrial fibrillation to assess the utilization of warfarin within 30 days of a first recorded diagnosis of atrial fibrillation or fluttter by risk of stroke*



*Hatched area represents the proportion of patients with uninterrupted therapy over 180 days following initial warfarin prescription

Zimetbaum PJ et al. Am J Med 2010;123:446-453

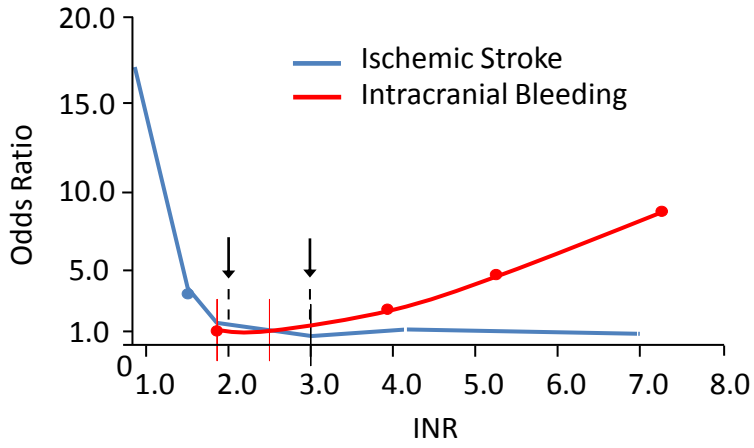
Average TTR of Warfarin-Treated Patients in the U.S.



ACC=Anticoagulation clinic, CI=Confidence interval, TTR=Time in therapeutic range

Baker WL et al. J Manage Care Pharm 2009;15:244-252

Warfarin is Limited By a Narrow Therapeutic Window



Ezekowitz MD et al. Mayo Clin Proc 2004;79:904-913
Haas S. J Thromb Thrombolysis 2008;25:52-60

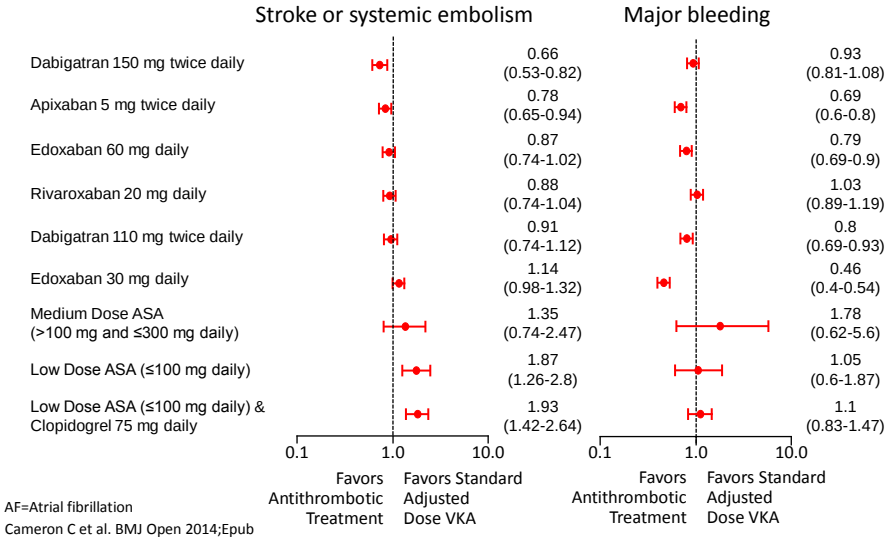
Other Reasons Why Clinicians Do Not Prescribe Warfarin

- Increased bleeding risk
- Stroke risk felt to be too low
- Monitoring inconvenience
- Impaired quality of life
- Aspirin is perceived to be a better option
- Cost of INR monitoring
- Doubted efficacy
- Unpredictable dose response
- Drug-drug interactions
- Drug-food interactions
- Delayed onset/offset
- Slow reversibility
- Patient reluctance
- Bad reputation among healthcare providers

McCrory DC et al. Arch Intern Med 1995;155:227-281
Ansell J et al. Chest 2008;133:160S-198S

Efficacy and Safety of Antithrombotic Therapy in AF

Systematic review of 16 randomized controlled trials of antithrombotic therapy in nonvalvular atrial fibrillation



AF=Atrial fibrillation

Cameron C et al. BMJ Open 2014;Epub

What About Another Approach to Stroke Reduction?

RESECTION OF THE LEFT AURICULAR APPENDIX

A Prophylaxis for Recurrent Arterial Emboli

JOHN L. MADDEN, M.D.
New York

A therapeutic problem which remains unsolved is the one pertaining to recurrent arterial emboli. Once a peripheral embolus has occurred there is a high incidence of recurrence. Unfortunately, all too frequently the recurrent embolus is fatal, commonly involving one of the cerebral arteries.[1] As Jefferson so aptly stated[2]: "In the nature of things a very high percentage of successes is unlikely ever to be attained, for emboli are apt to be multiple and further infarction will sometimes carry off the patient in whom a local success has been won."

Since a thrombus is the precursor of every arterial embolus, the ideal prophylaxis for recurrent arterial emboli should be the removal of the thrombus together with its site of origin. Rheumatic mitral stenosis is one of the commonest causes of a peripheral arterial embolus, an embolus occurring in approximately 45 per cent of the cases.[10] In this disease the embolus originates as a mural thrombus within the left auricle or its appendix, more commonly the latter.

Examination disclosed an embolic occlusion of the left common iliac artery. The heart was not decompensated. Approximately twenty hours after the onset of symptoms a transperitoneal embolectomy was performed successfully.

The patient was admitted to the hospital for the second time on Jan. 11, 1948 (fifteen month interval), complaining of numbness and tingling in the right leg of two hours' duration. In the interval between admissions to the hospital manifestations of congestive heart failure occurred several times, but the symptoms abated after an increase in the maintenance dose of digitalis.

Examination showed an embolic occlusion of the right popliteal artery. About five hours after the onset of symptoms the embolus was removed successfully.

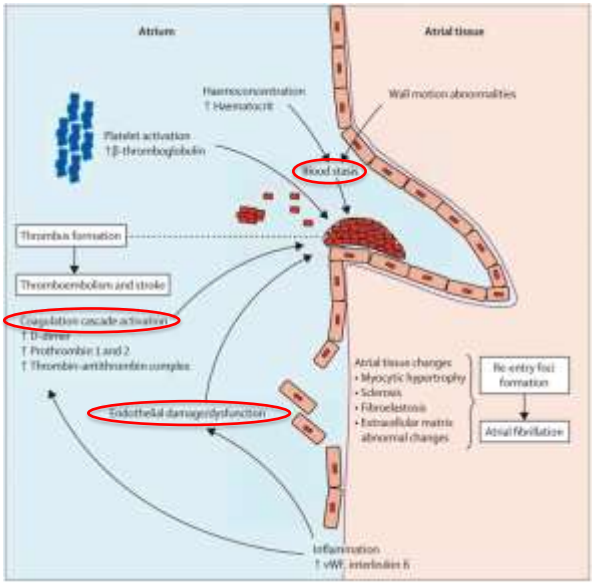
In view of the history of chronic rheumatic heart disease with mitral stenosis, auricular fibrillation and recurrent peripheral arterial emboli, a resection of the left auricular appendix was advised. On February 21, with intratracheal anesthesia (gas, oxygen and ether) a resection of the left auricular appendix was performed.

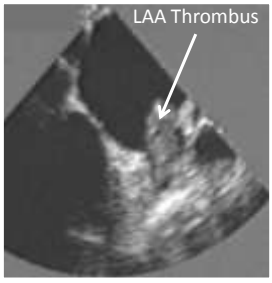
During the operation stoppage of the heart occurred. Immediate manual massage of the heart was begun concomitant with the maintenance of artificial respiration by a rhythmic compression of the breathing bag. The recovery of the patient was complete.

An examination immediately postoperative revealed a left hemiparesis, which was believed to be secondary to a right cerebral embolus. Subsequently, a decided personality change was observed, which persisted throughout the stay in the hospital.

Madden JL. JAMA 1949;140:769-772

Why Target the Left Atrial Appendage?





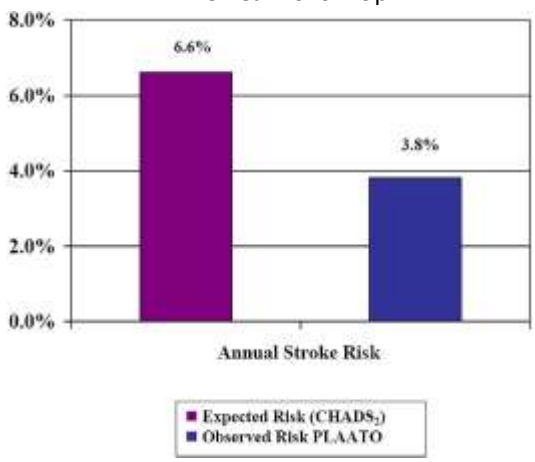
Watson T et al. Lancet 2009;373:155-166
Figure reproduced with permission. Copyright 1988, American Heart Association. Courtesy of J Reiffel.

Transcatheter Closure—PLAATO System*

An observational study of 64 patients with paroxysmal atrial fibrillation treated with percutaneous left atrial appendage transcatheter occlusion

Self-expanding nitinol cage covered with an expanded PTFE membrane

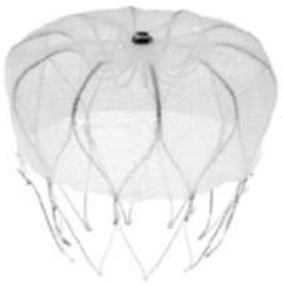
5-Year Follow Up



*Not FDA approved
PTFE=Polytetrafluoroethylene
Block PC et al. JACC Cardiovasc Interv 2009;2:594-600

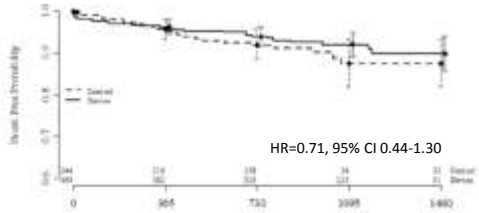
Transcatheter Closure—Watchman Device*

707 patients with nonvalular AF and at least 1 risk factor for stroke randomized to the Watchman device or warfarin for a mean of 2.3 years (PROTECT AF Trial)

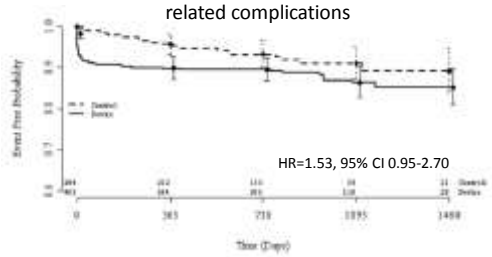


Self-expanding nitinol frame and membrane cap

Stroke, systemic embolism, and CV death



Composite of major bleeding or procedure-related complications

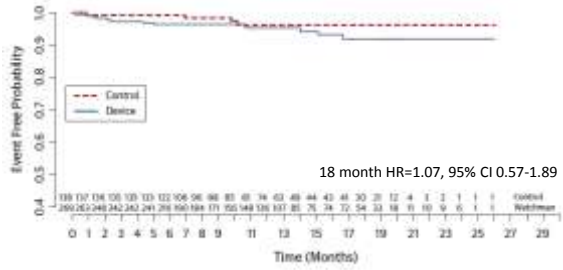


*Not FDA approved
AF=Atrial fibrillation, CV=Cardiovascular
Reddy VY et al. Circulation 2013;127:720-729

Transcatheter Closure—Watchman Device*

407 patients with nonvalular atrial fibrillation and and a $CHADS_2$ score ≥ 2 or a score of 1 with at least 1 risk factor for stroke randomized to the Watchman device or warfarin for a mean of 18 months (PREVAIL Trial)

Stroke, systemic embolism, and cardiovascular death



Procedure-related complications

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

*Not FDA approved
Holmes Jr. DR et al. JACC 2014;64:1-12

Transcatheter Closure—Amplatzer Cardiac Plug*

Two observational studies of 111 patients with paroxysmal atrial fibrillation and ≥1 additional risk factor for stroke with a contraindication to anticoagulation treated with the Amplatzer cardiac plug

Self-expanding nitinol mesh with a distal lobe and proximal disk connected by a short central waist

91 Implant Years of Follow Up

MAE	Patients (n = 111)
Major or minor stroke	2
Myocardial infarction	0
Requirement for cardiovascular surgery related to PLAATO procedure	1
Cardiac or neurological death	4
Any MAE	7 (in 5 patients)

MAE = major adverse event.

Transesophageal Doppler Color Flow	Angiography			
	Severe Leak	Moderate Leak	Mild Leak	Trace to Absent Leak
Severe leak	—	—	—	—
Moderate leak	—	—	—	2 pts
Mild leak	—	—	5 pts	15 pts
Trace to absent leak	—	—	8 pts	58 pts

*Not FDA approved

Ostermayer SH et al. JACC 2005;46:9-14

Transcatheter Closure—Lariat Device*

Retrospective study of 154 patients with nonvalvular atrial fibrillation treated with left atrial suture ligation

Combined trans-septal and subxiphoid approach to deliver a surgical suture ligation

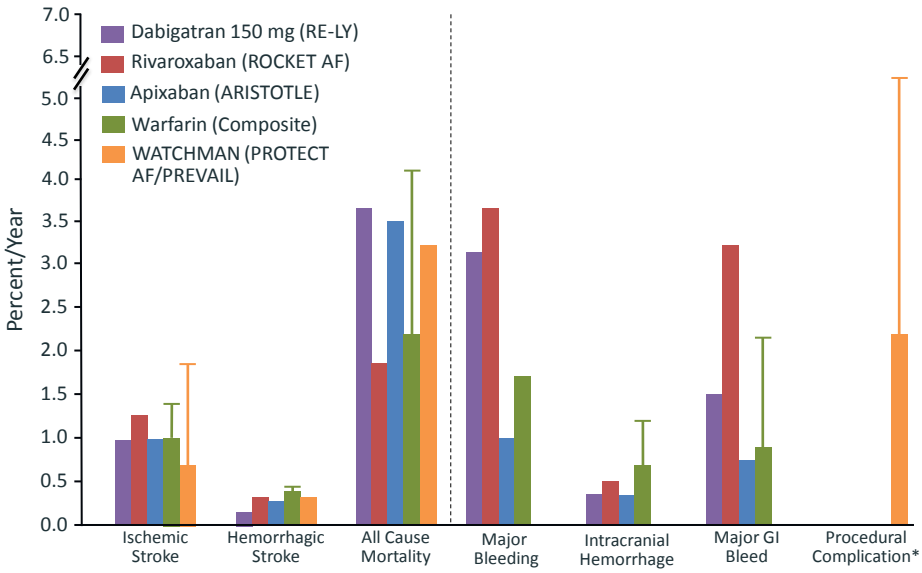
Median of 4 Months Follow Up

Major bleed	14 (9.1)
Any transfusion with overt bleeding	7 (4.5)
Overt bleed, hemoglobin drop 3 to <5 g/dl	5 (3.2)
Overt bleed, hemoglobin drop ≥5 g/dl	3 (1.9)
Cardiac tamponade	7 (4.5)
Bleeding requiring surgical control	2 (1.3)
Bleeding requiring vasoactive agents	4 (2.6)
Fatal bleeding	0
Lariat unable to be deployed	9 (48)
Pericardial adhesions	5
LAA anatomy	2
Aborted procedure after RV perforation	2
Residual Leak ≥ 5 mm	1 (6)
Major complication before discharge	15 (71)

*Not FDA approved

Ostermayer SH et al. JACC 2005;46:9-14

How Does Percutaneous LAA Closure Fare?



*Includes device-related major bleed, pericardial tamponade, device embolization
LAA=Left atrial appendage

Surgical Closure—LAAOS III Study

A randomized study of 4700 patients with atrial fibrillation undergoing cardiac surgery randomized to surgical resection of the left atrial appendage versus placebo with anticipated follow up for 4 years

Annual rates of stroke or systemic embolism in current antithrombotic trials

Aspirin, ACTIVE A (45) [3,782]	3.7	Warfarin, ACTIVE W (48) [3,371]	1.5
Aspirin, AVERROES (46) [2,791]	3.5	Warfarin, RELY (49) [6,022]	1.7
Aspirin and Plavix, ACTIVE A (45) [3,772]	2.8	Warfarin, ARISTOTLE (47) [9,081]	1.6
Apixaban, ARISTOTLE (47) [9,120]	1.3	Dabigatran 150 mg, RELY (49) [6,076]	1.1
Apixaban, AVERROES (46) [2,808]	1.6	Dabigatran 110 mg, RELY (49) [6,015]	1.5

Expected event rates and RRR with LAA occlusion on top of usual care

Therapy component of usual care	% patients years on therapy component	Control rate of primary outcome per year	Expected relative risk reduction with LAA occlusion (%)	Treatment rate of primary outcome per year
No antithrombotic	5	5.1	63	1.9
Antiplatelet	30	3.7	63	1.4
Warfarin	45	1.7	25	1.3
Novel anticoagulant	20	1.5	25	1.1
Overall usual care	100	2.5	36	1.6

LAA, left atrial appendage.

LAA=Left atrial appendage, RRR=Relative risk reduction
Whitlock R et al. Ann Cardiothorac Surg 2014;3:45-54

Where Do LAA Closure Devices Currently Sit?

- Currently, no percutaneous closure devices are FDA approved for stroke reduction in atrial fibrillation.
- Closure devices have not been compared to the NOACs.
- A closure device should only be considered after factoring in:
  - The patient's overall health
  - The patient's ability to tolerate oral anticoagulation therapy
  - The procedural risks and operator's experience
- Closure devices should be considered for those at high risk for oral anticoagulant related bleeding complications.
  - These individuals were excluded from the PROTECT AF and PREVAIL studies
  - In these trials, patients were treated with warfarin plus aspirin for 45 days
- The long term safety of closure devices is still unknown.
  - Late risks include thrombus formation and progression of leak size

LAA=Left atrial appendage

Lee RJ et al. JACC 2014;64:13-15