

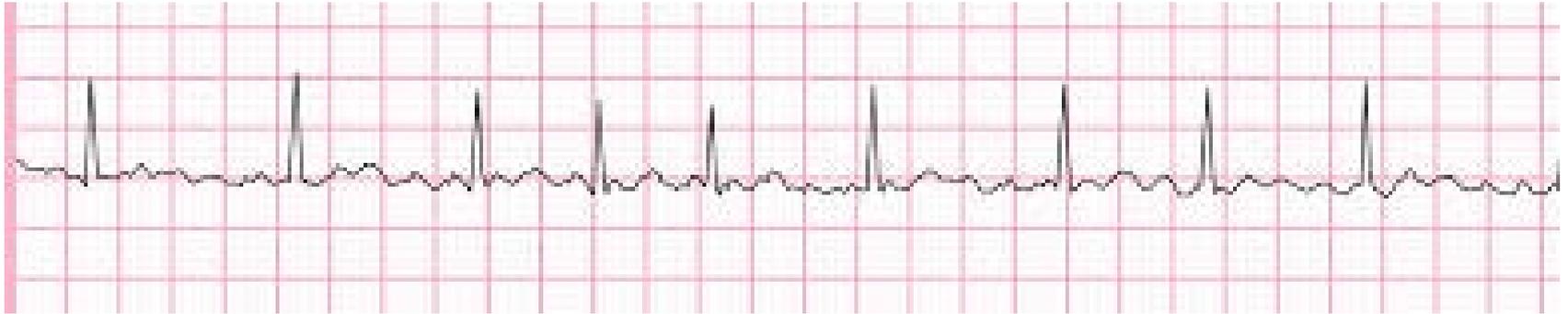
Stroke Prevention in Non Valvular Atrial Fibrillation

Emphasis on left atrial appendage closure.

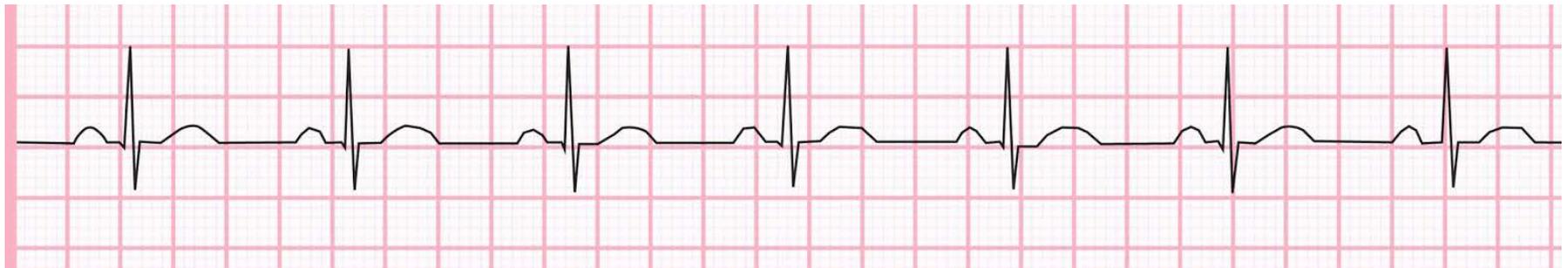
Atrial Fibrillation and Stroke Prevention

1. What is atrial fibrillation?
2. How does atrial fibrillation cause stroke?
3. How long should one be in atrial fibrillation to develop stroke?
4. What is the risk of stroke?
5. How can we prevent stroke?
6. What is the risk of bleeding ?
7. What if one cannot take blood thinner due to bleeding risk?
8. What are the indications, success and complications of left atrial appendage closure.

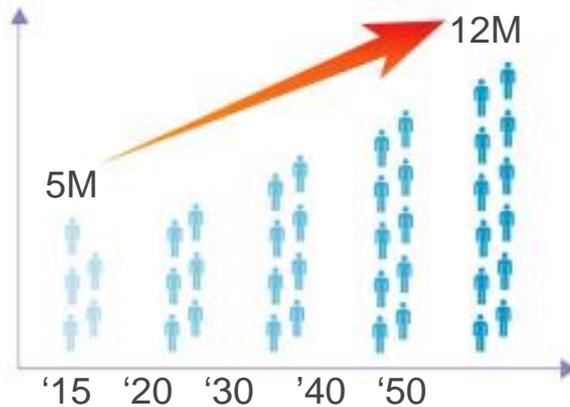
Atrial fibrillation



Normal Sinus Rhythm



Atrial Fibrillation Prevalence



~5M

people with AF in U.S.,
expected to more than double
by 2050¹

5X

increased risk of stroke
for AF patients²

AF



1 in 6 strokes occur in
patients with AF³



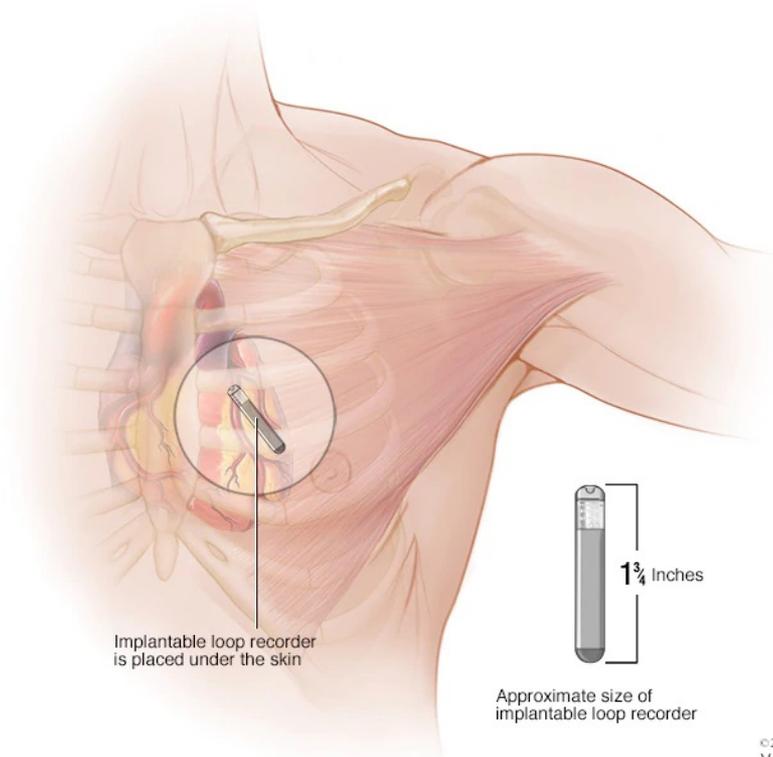
47% of AF patients experiencing a
stroke will **suffer a second stroke**
within 6 months⁴

1. Go AS, et al, Heart Disease and Stroke Statistics—2013 Update: A Report From the American Heart Association. *Circulation*. 2013; 127: e6-e245.
 2. Holmes DR, Atrial Fibrillation and Stroke Management: Present and Future, *Seminars in Neurology* 2010;30:528–536
 3. Hart RG, Halperin JL. Atrial fibrillation and thromboembolism: a decade of progress in stroke prevention. *Ann Intern Med*. 1999.
 4. Wolf PA et al, Duration of Atrial Fibrillation and the Imminence of Stroke: The Framingham Study, *Stroke* 1983; 14:664-667

Type of atrial fibrillation

- **Paroxysmal AF:** Episodes of AF that terminate spontaneously within 7 days (most episodes last less than 24 hours).
- **Persistent AF:** Episodes of AF that last more than 7 days and may require either pharmacologic or electrical intervention to terminate.
- **Long-standing persistent AF:** AF that has persisted for more than 12 months, either because cardioversion has failed or because cardioversion has not been attempted.
- **Permanent AF:** When both patient and clinician have decided to abort any further restoration strategies after shared clinical decision making

Monitoring for Atrial fibrillation in Cryptogenic Stroke



Implantable Loop Monitor
Duration of Monitor is 2 years

Mobile Telemetry or Event monitor
Duration of Monitor is 30 days

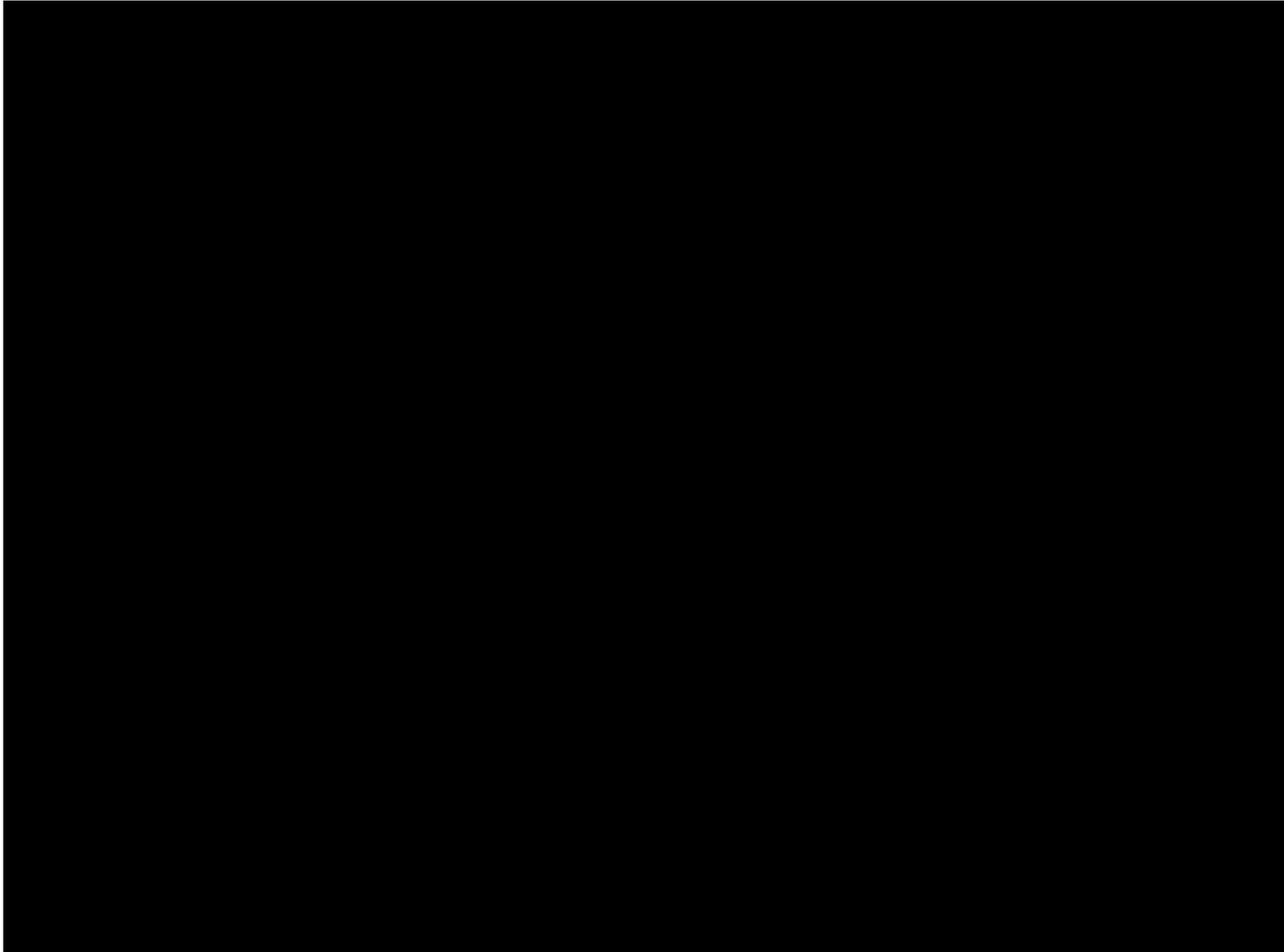
Atrial fibrillation-Related Stroke and the Left Atrial Appendage

- In non-valvular AF, >90% of stroke-causing clots that come from the left atrium are formed in the LAA³.

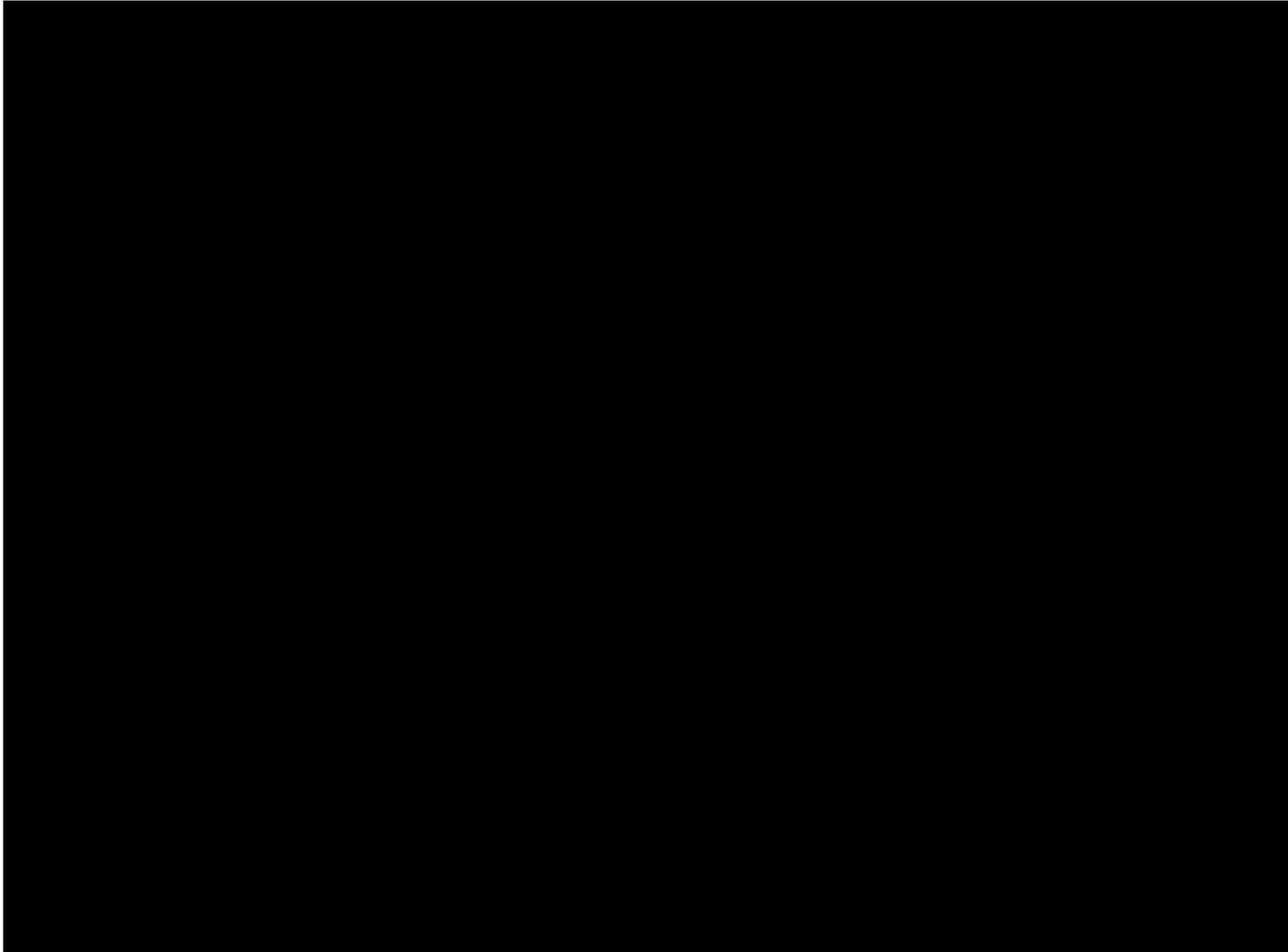


1. Stoddard et al. Am Heart J. (2003)
2. Goldman et al. J Am Soc Echocardiogr (1999)
3. Blackshear JL, Odell JA., *Annals of Thoracic Surg* (1996)

Left atrial appendage thrombus

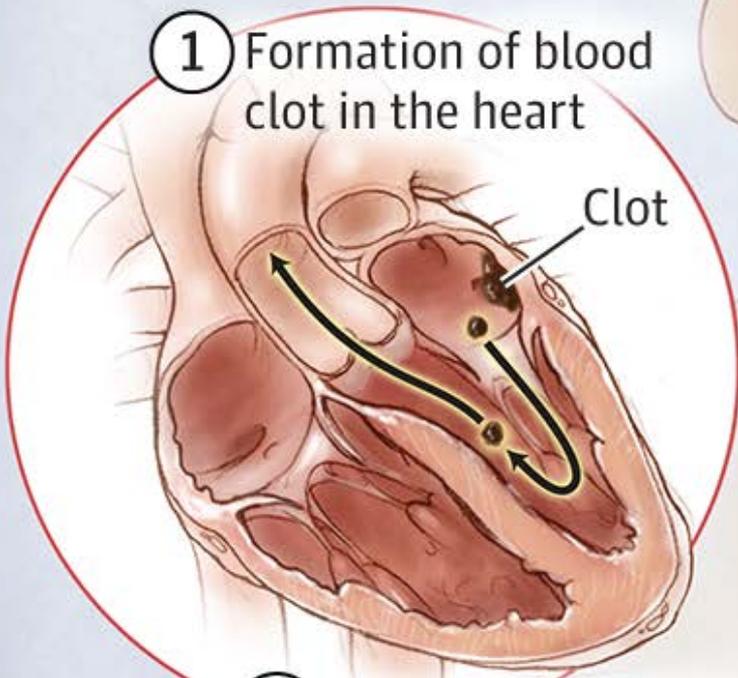


Left atrial thrombus



Atrial Fibrillation

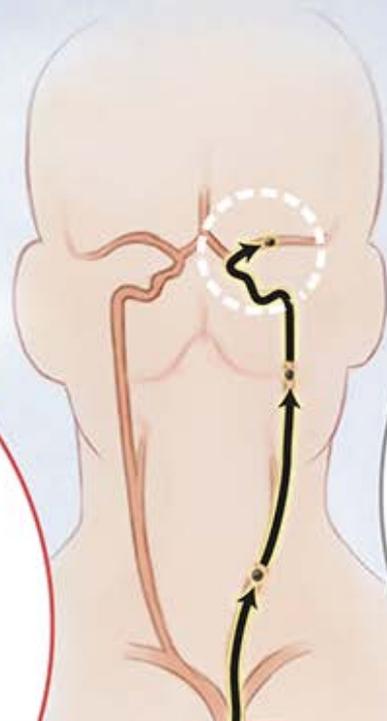
- 1 Formation of blood clot in the heart



- 2 Blood clot travels through the heart

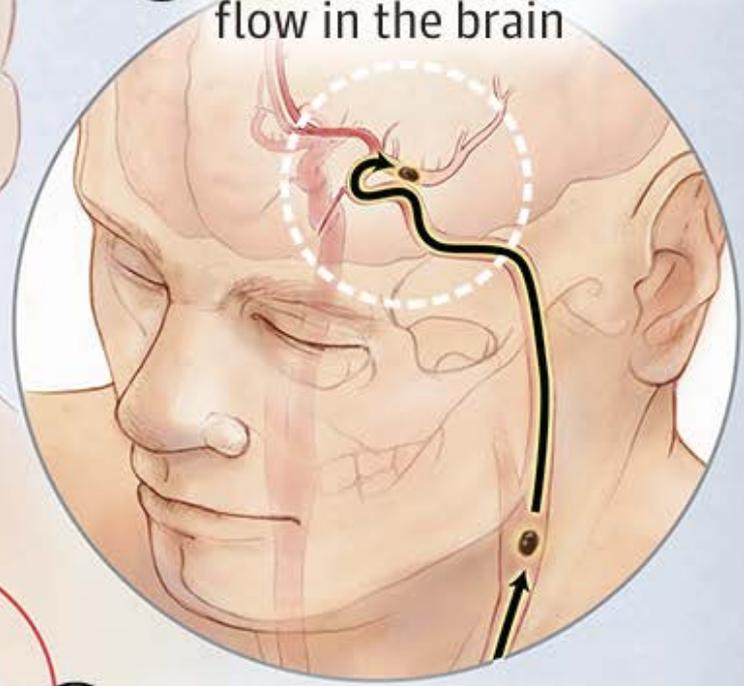


- 3 Blood clot travels from the heart to the brain



Ischemic Stroke

- 4 Blood clot blocks blood flow in the brain



CHA₂DS₂-VASc Risk Stratification Scores for Subjects With Nonvalvular AF

Definition and Scores for CHA ₂ DS ₂ -VASc	
Congestive HF	1
Hypertension	1
Age ≥75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65–74 y	1
Sex category (i.e., female sex)	1
Maximum score	9

Stroke Risk Stratification With CHA ₂ DS ₂ -VASc Scores	
CHA ₂ DS ₂ -VASc†	
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	15.20

HAS-BLED score

Condition	Points
H - Hypertension	1
A - Abnormal renal or liver function (1 point each)	1 or 2
S - Stroke	1
B - Bleeding	1
L - Labile INRs	1
E - Elderly (> 65 years)	1
D - Drugs or alcohol (1 point each)	1 or 2

HAS-BLED score	Bleeds per 100 patient-years
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.5

Note: HAS-BLED has been validated for warfarin, but not for the new anticoagulants.

Risk-Based Antithrombotic Therapy

Recommendations

CHA2DS2-VASc score of 2 or greater in men

CHA2DS2-VASc score of 3 or greater in women

Recommend anticoagulation:

- Warfarin
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban

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

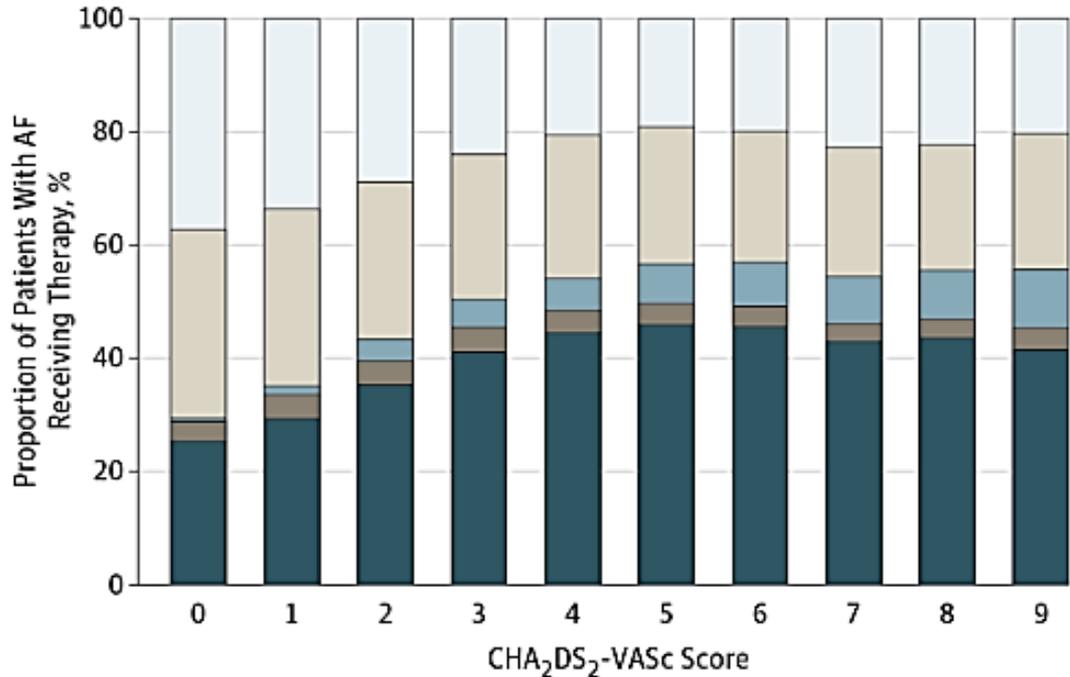
Options to prevent stroke in non valvular A.fib

Drug	Year	Mechanism of action	Reversal agents
Aspirin	1800's	Antiplatelet	
Warfarin	1944	Multiple factors	FFP/Vit K/PCC
Dabigatran	2010	Thrombin	idarucizumab
Rivaroxiban	2011	Xa	andexanet alfa
Apixaban	2012	Xa	andexanet alfa
Edoxaban	2015	Xa	andexanet alfa
Left atrial appendage occlusion/Closure	2015 (watchman)	Mechanical	

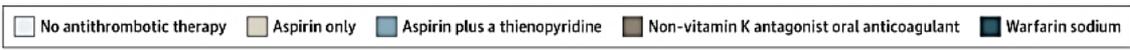
Oral Anticoagulation

NCDR Pinnacle Registry

Use of OACs in AF Patients peaks at ~50%,
use declines with increasing risk



No. 12348 36976 61557 87008 97878 70212 37314 17814 6385 1161



Warfarin

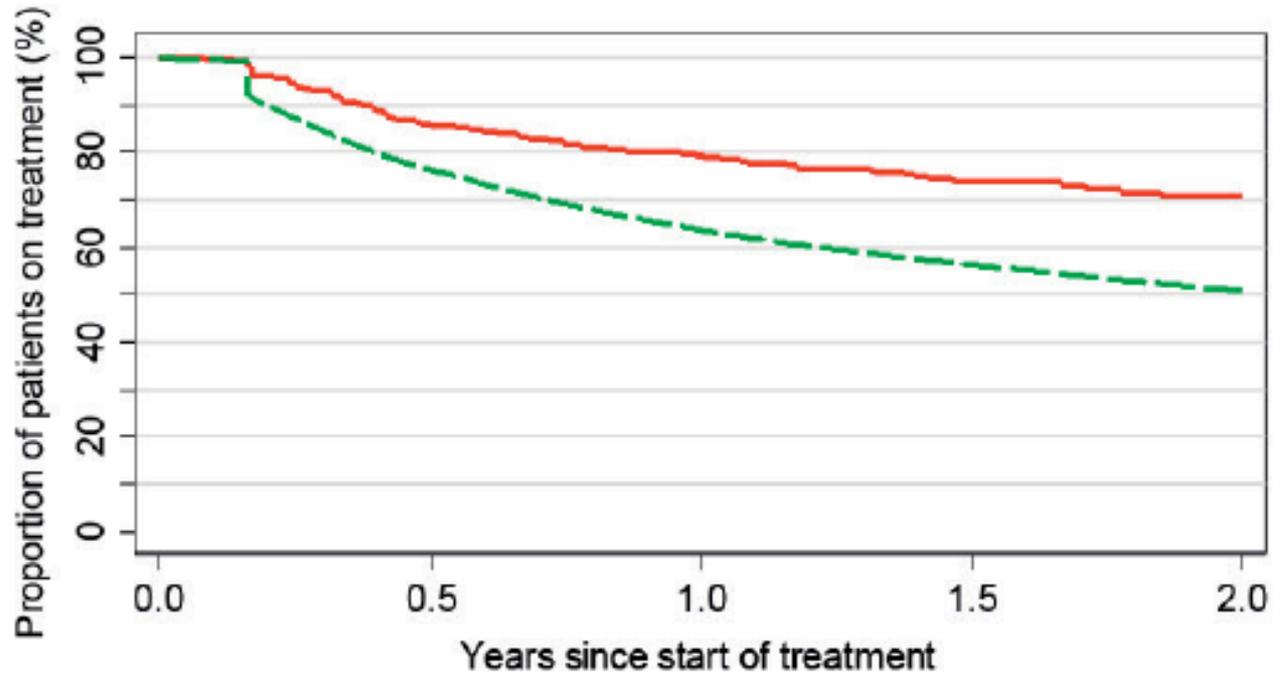
- Bleeding risk
- Daily regimen
- High non-adherence rates
- Regular INR monitoring
- Food and drug interaction issues
- Complicates surgical procedures

Novel Oral Anticoagulants

- Bleeding risk
- Daily or 2x/daily regimen
- High non-adherence rates
- Complicates surgical procedures
- High cost

Despite NOAC Adoption and Ability to Switch NOACs, Adherence to Anticoagulation Remains a Challenge

~30% of NOAC patients stop taking any drug at 2 years



NOAC	914	651	342	139	41
VKA	12307	8453	5762	3915	2506

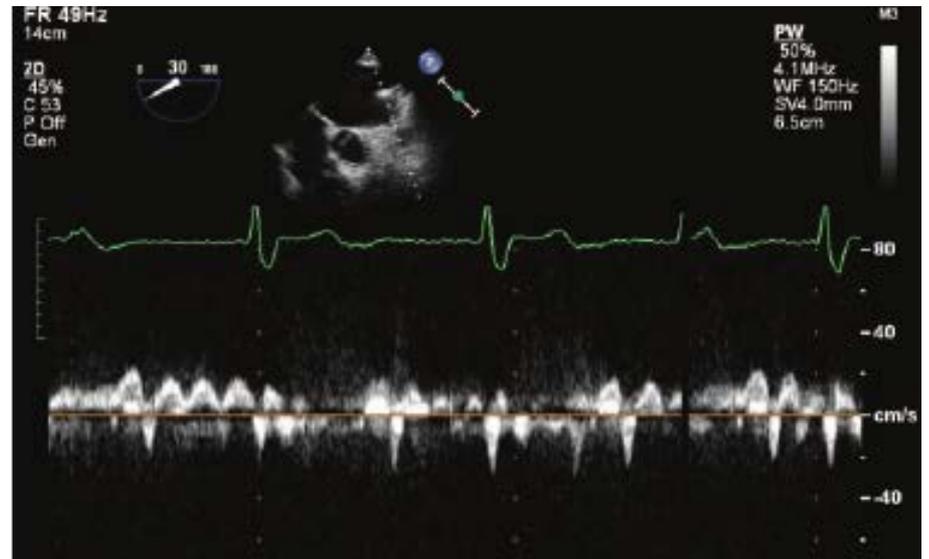
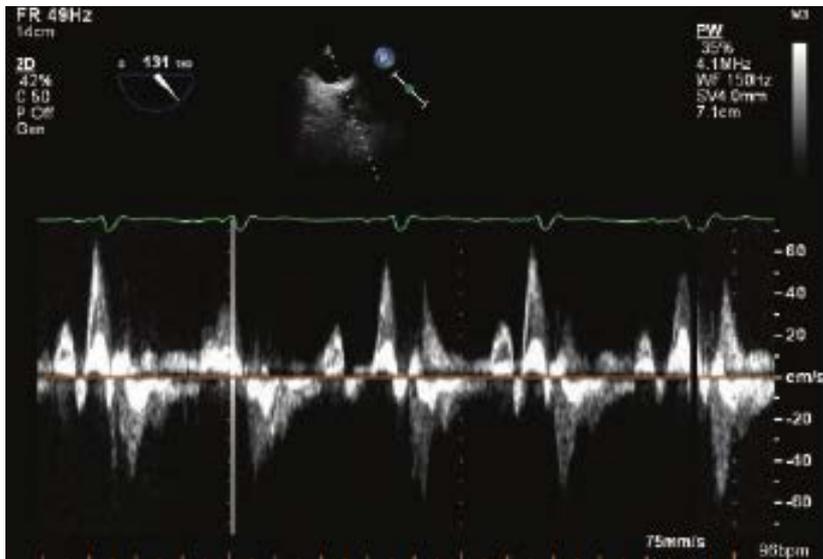
Patients with AF at high stroke risk with High risk bleeding under anticoagulation.

1. **Coagulopathies**—low platelet counts, myelodysplastic syndrome (MDS)
2. **Inherited bleeding disorder**—Von Willebrand disease, haemophilia
3. **Severe hepatic or renal dysfunction**— Alcoholic liver cirrhosis,
4. **Vascular disease or malformations**— Intestinal angiodysplasia, intracerebral haemorrhage, cerebral microbleeds (~amyloid angiopathy), retinal vasculopathy, CNS aneurysms.
5. **GI disease with bleeding**—Neoplastic disease, intestinal angiodysplasia, Ulcerative colitis, Diverticulosis, peptic ulcer disease.
6. **High probability of frequent and/or severe traumas**—Epilepsy, in the elderly, Parkinson's disease, orthostatic hypotension.
7. **Ischaemic stroke despite well-controlled OAC therapy.** Probability of therapeutic non-compliance to (N)OAC. Intolerance to (N)OAC drugs—GI intolerance, severe liver/kidney dysfunction, drug interactions.

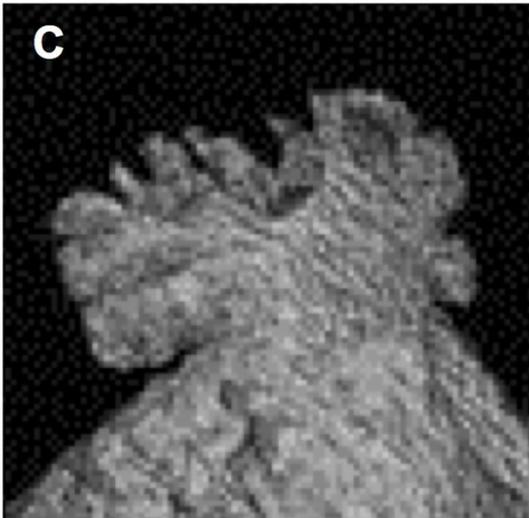
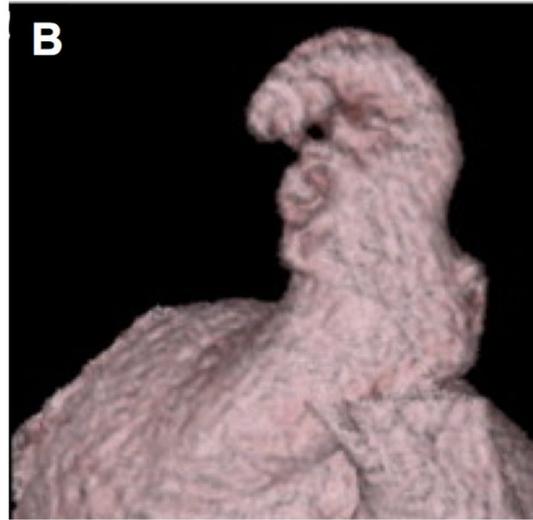
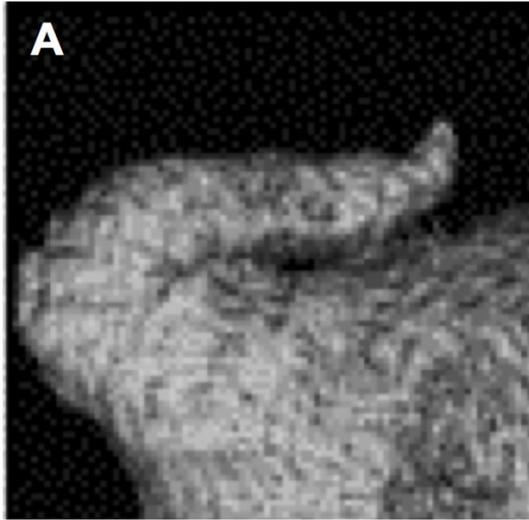
Device-Based Alternative for Stroke Risk Reduction

Left atrial appedage closure/occlusion devices

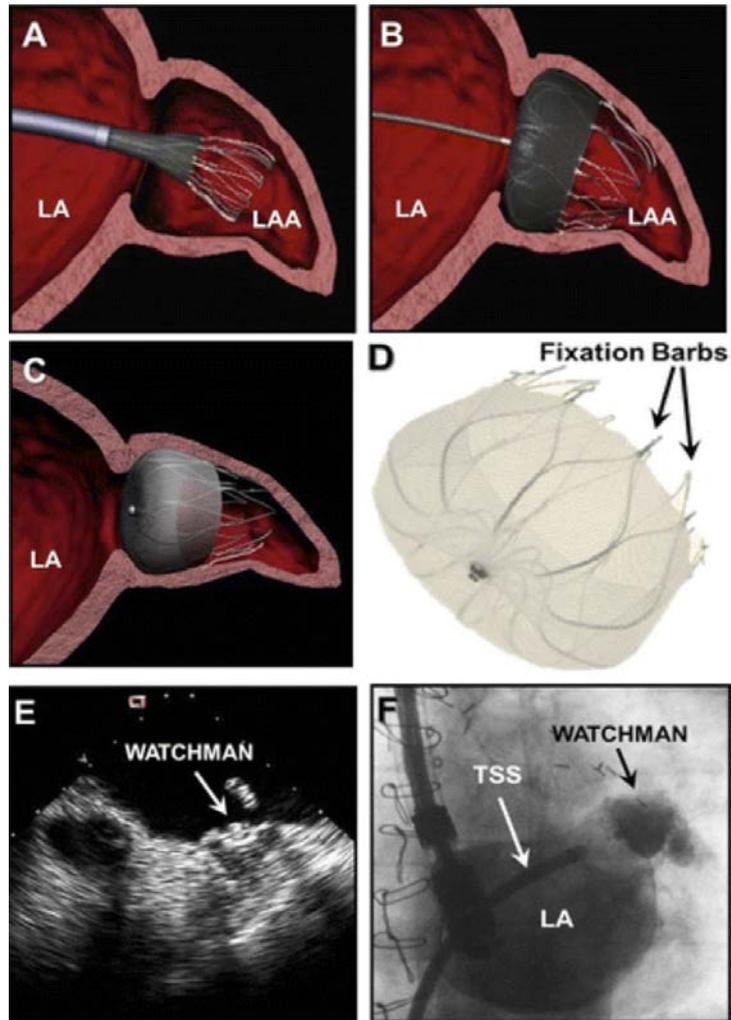
Left atrial appendage velocities in atrial fibrillation



Left atrial appendage morphology



WATCHMAN device.



Criteria for watchman device

INCREASED RISK FOR STROKE

- CHA2DS2-VASc score ≥ 3

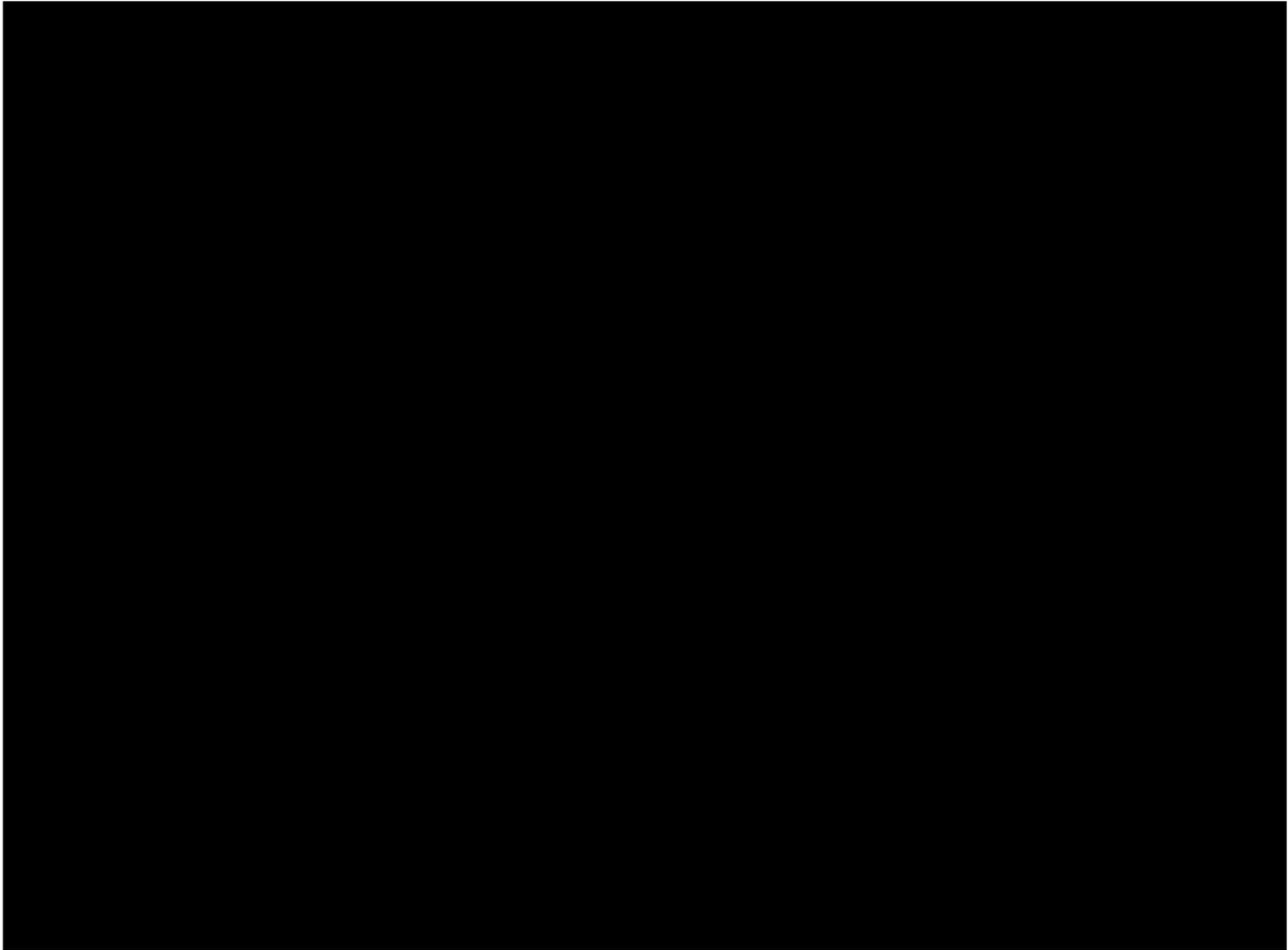
• **SUITABLE FOR SHORT-TERM WARFARIN**

- But deemed unable to take long-term oral anticoagulation

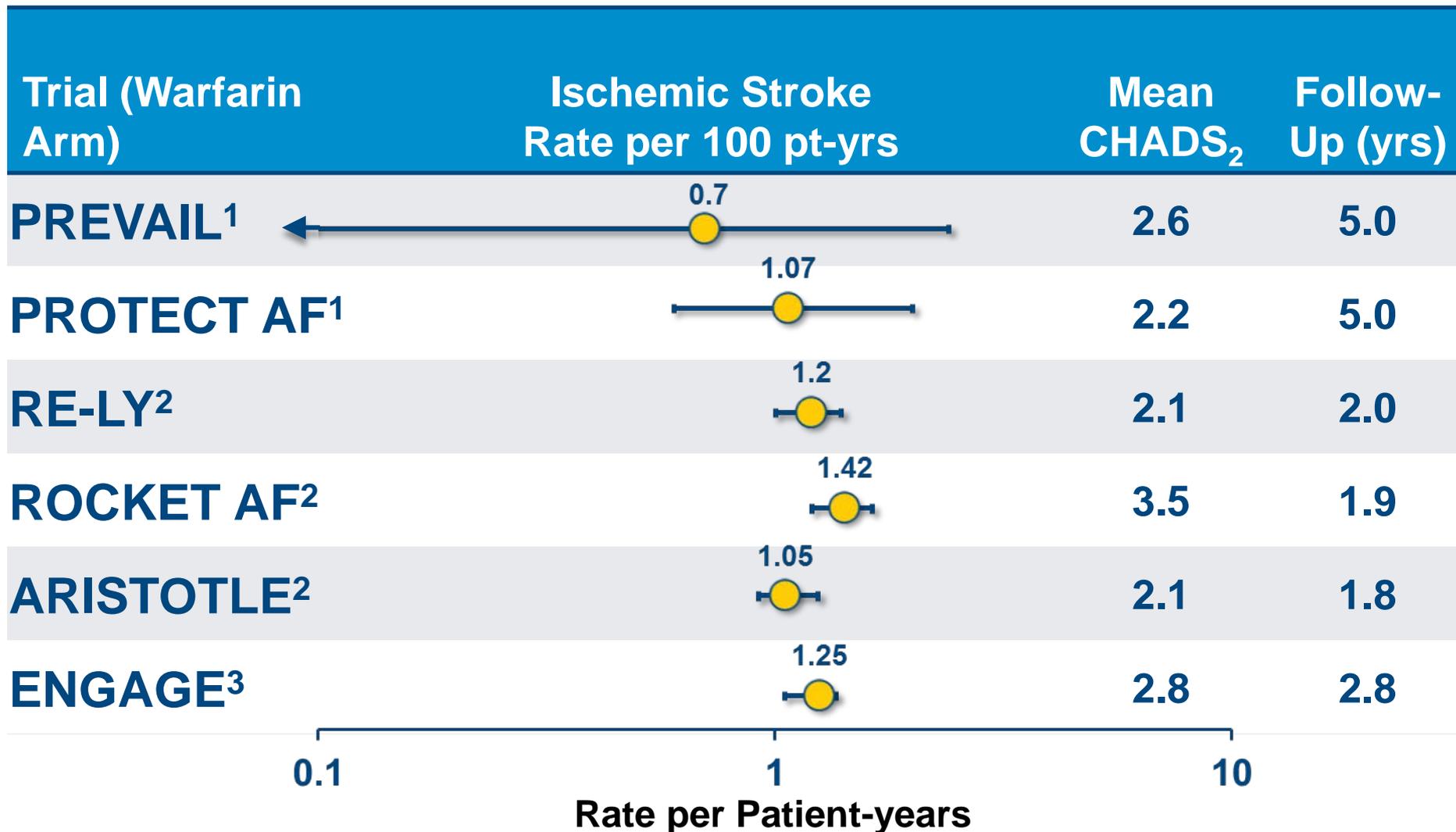
• **FORMAL SHARED DECISION MAKING INTERACTION**

- Documented evidence of a formal interaction between the patient and an independent non-interventional physician using an OAC evidence-based decision tool

Watchman

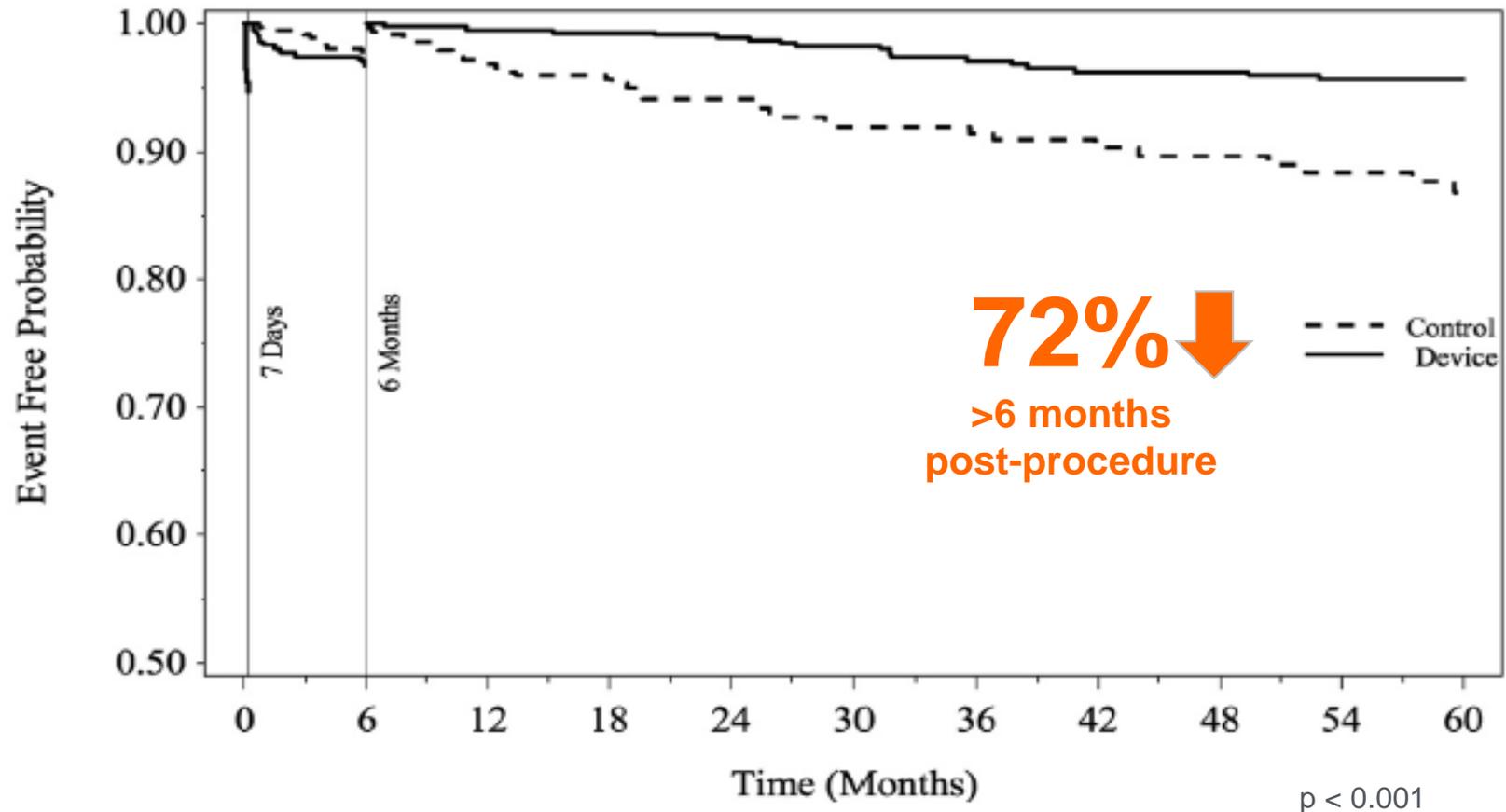


Warfarin Ischemic Stroke Rate in PREVAIL

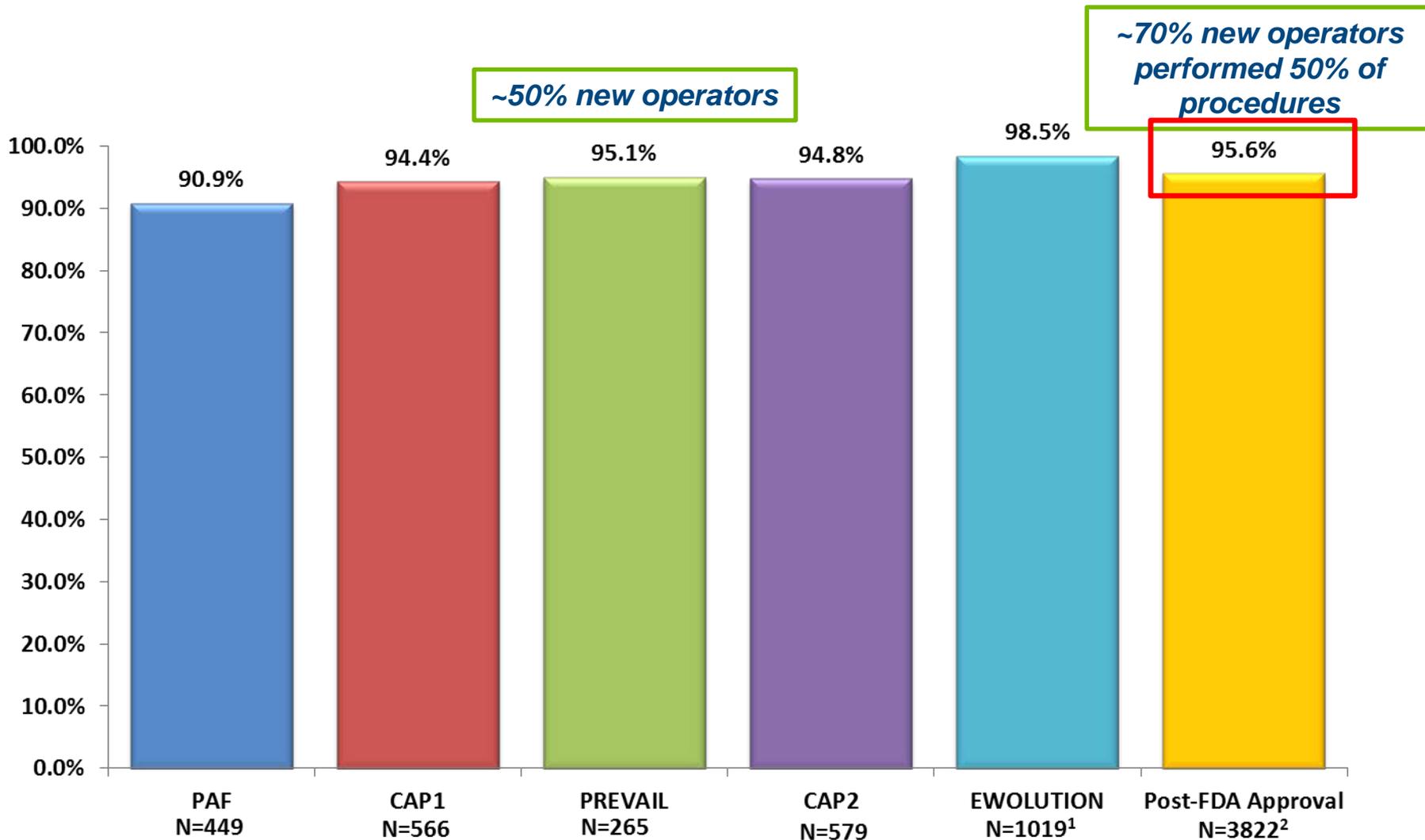


Bleeding Outcomes after Left Atrial Appendage Closure Compared with Long-term Warfarin

Freedom of Major Bleeding Over 3 Adjunctive Pharmacotherapy Intervals



Procedural Success

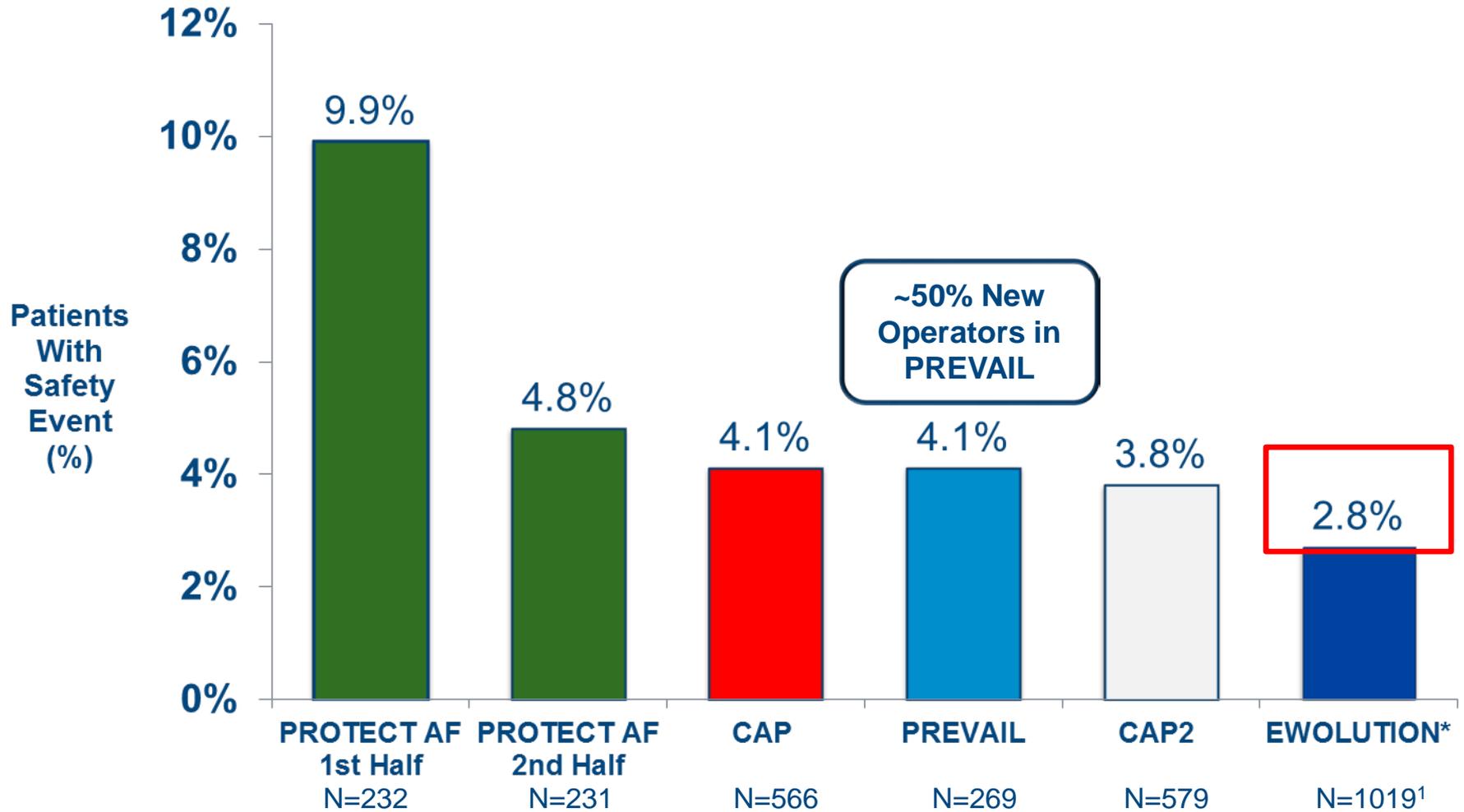


Implant success defined as deployment and release of the device into the LAA; no leak ≥ 5 mm

* The EWOLUTION Registry is a European prospective registry which reflects CE Mark indications for use which differ from the FDA indications for use.

¹ Boersma, L. et al. *EHJ* 2016;37(31): 2465.; ² Reddy VY, Holmes DR, et al. *JACC* 2016; 69(3): 253-261.

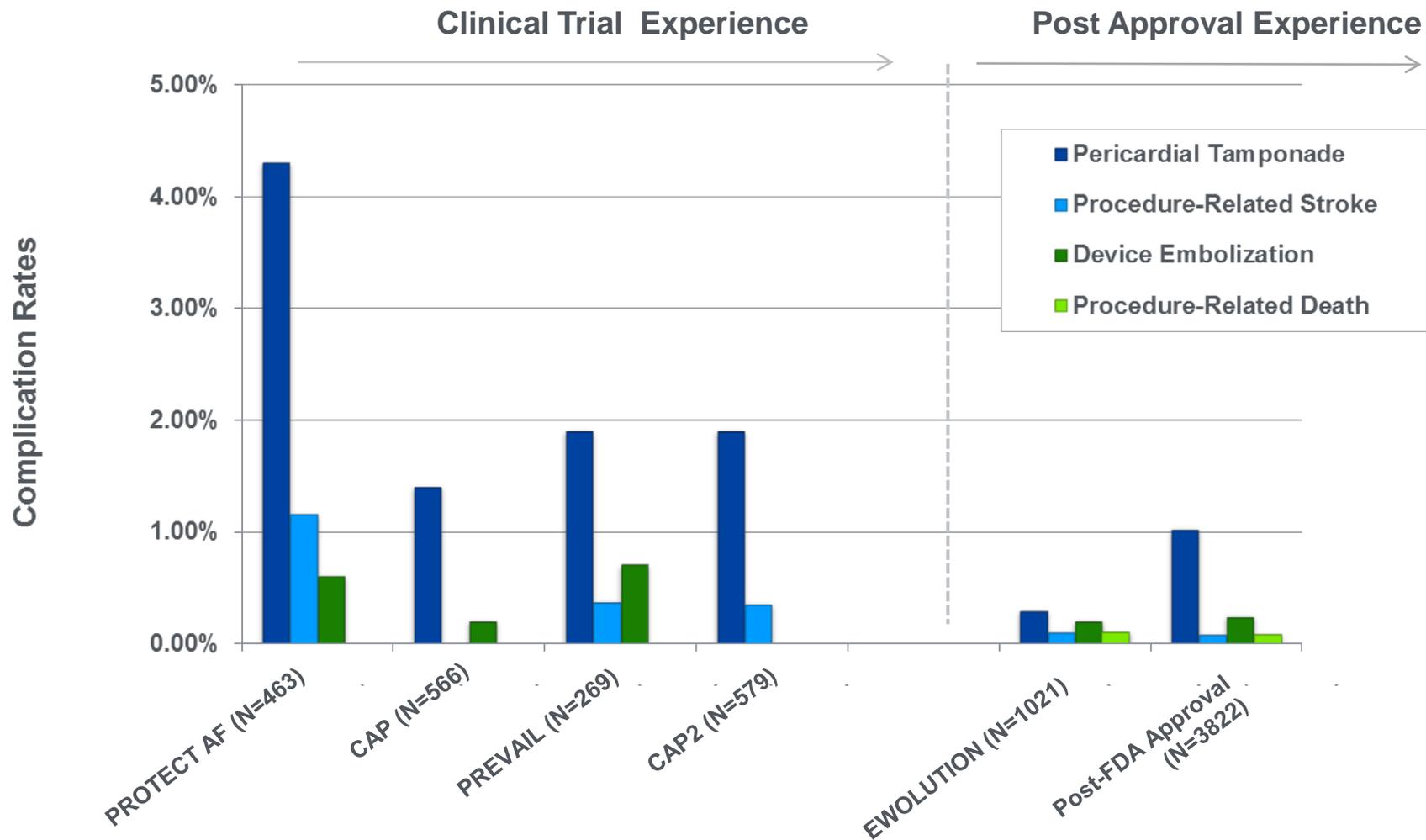
All Device and/or Procedure-related Serious Adverse Events within 7 Days



* The EWOLUTION Registry is a European prospective registry which reflects CE Mark indications for use which differ from the FDA indications for use.

¹ Boersma, LVA.et al. *EHJ* 2016; 37(31): 2465.

Real World Data: Post-FDA Approval Major Procedural Complications

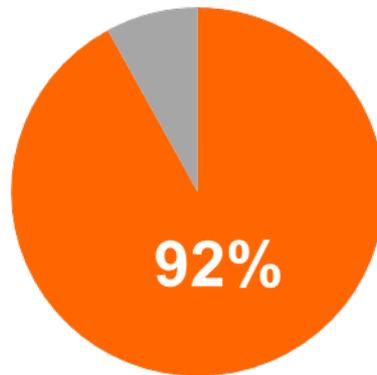


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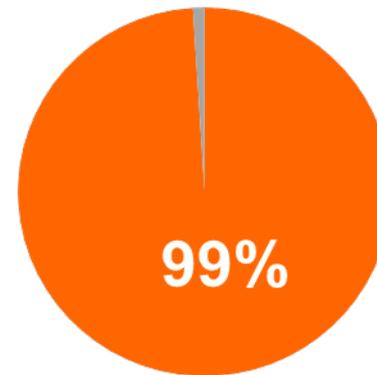
Reddy VY, Holmes DR, et al. JACC 2016; 69(3): 253-261.

Patients that Discontinue Long-term OAC

92% of patients were able to discontinue warfarin after 45 days, with >99% able to discontinue after 1 year³



45 Days

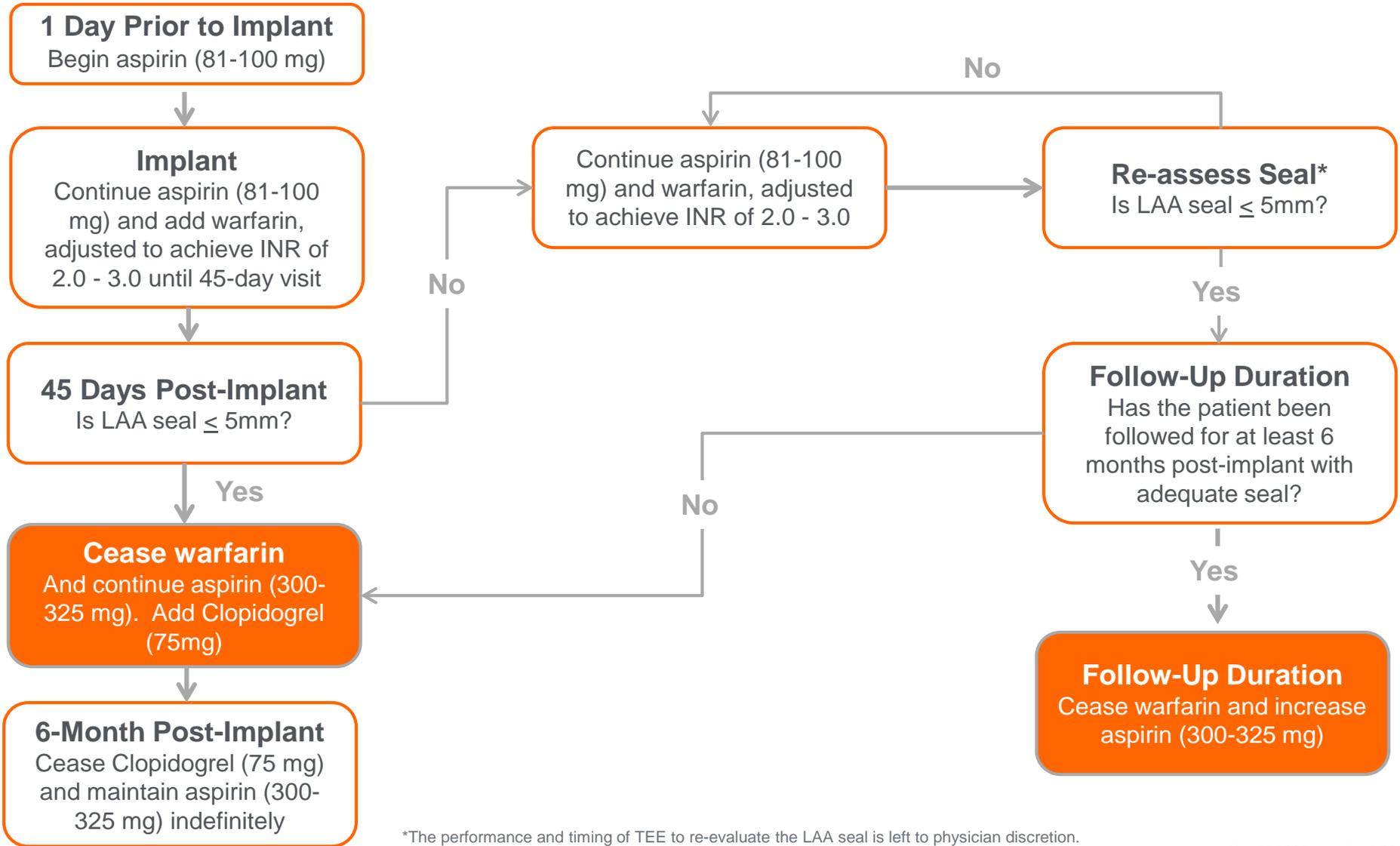


1 Year

Warfarin Cessation with WATCHMAN

Study*	45-day	12-month
PROTECT AF ¹	87%	>93%
CAP ²	96%	>96%
PREVAIL ³	92%	>99%

WATCHMAN Implant Procedure



*The performance and timing of TEE to re-evaluate the LAA seal is left to physician discretion. Typical to patient treatment in U.S. clinical trials

LAAC Device with Long-term Clinical Data

Results		
Safety	Procedure is safe	95% implant success; ~1.5% complication rates ¹
Primary Efficacy	Comparable to warfarin	18% reduction in events (p=0.27) ²
Stroke	Comparable to warfarin	55% reduction in disabling/fatal stroke (p=0.03)*, largely driven by 80% reduction in hemorrhagic stroke (p=0.003) ²
Mortality	Compared to warfarin	27% reduction in all-cause mortality (p=0.04) ² 41% reduction in CV/unexplained mortality (p=0.03) ²
Major Bleeding	Compared to warfarin post-procedure	72% reduction after 6-months (p=0.001) ³
Warfarin Cessation		92% of patients discontinue after 45-days; 99% of patients discontinue after 1 year ⁴

1. Varosy P et al. JACC 2018; *In press.*; 2 Reddy VY et al. JACC. 2017; *In Press*; 3. Price, M. J., V. Y. Reddy, et al. JACC: CV Interv 2015; 8(15): 1925-1932; 4. Holmes, DR et al. JACC 2014; 64(1): 1-12; 6.

Contraindication for LAA closure device

- Low risk for stroke $CHA_{(2)}DS_2-(VASc)=0$
- Valvular heart disease (eg, Severe mitral stenosis)
- Other indications for long-term or lifelong OAC—mechanical prosthetic valve, pulmonary embolism and deep vein thrombosis, thrombi in the left atrium or ventricle
- Contraindications for transseptal catheterisation—left atrial thrombus or tumour, active infection, uncooperative patient, (presence of ASD/PFO closure device)