Current status and future perspectives of LAA closure

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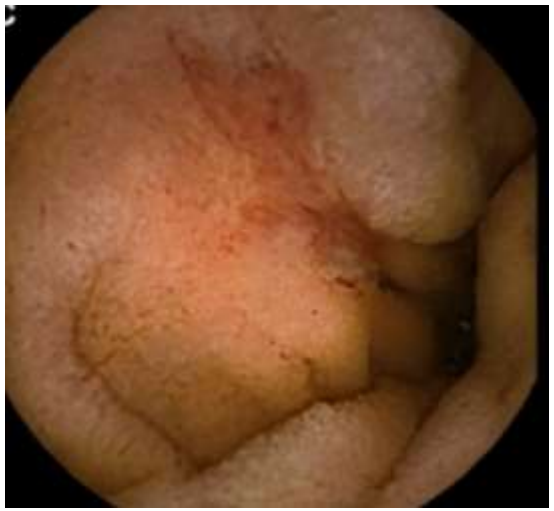
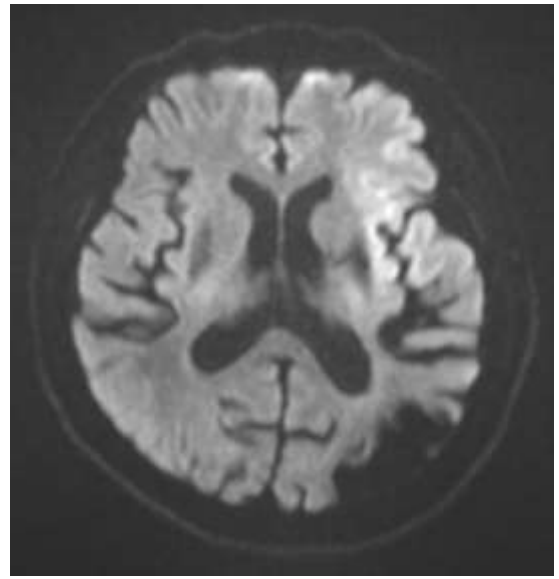
Case

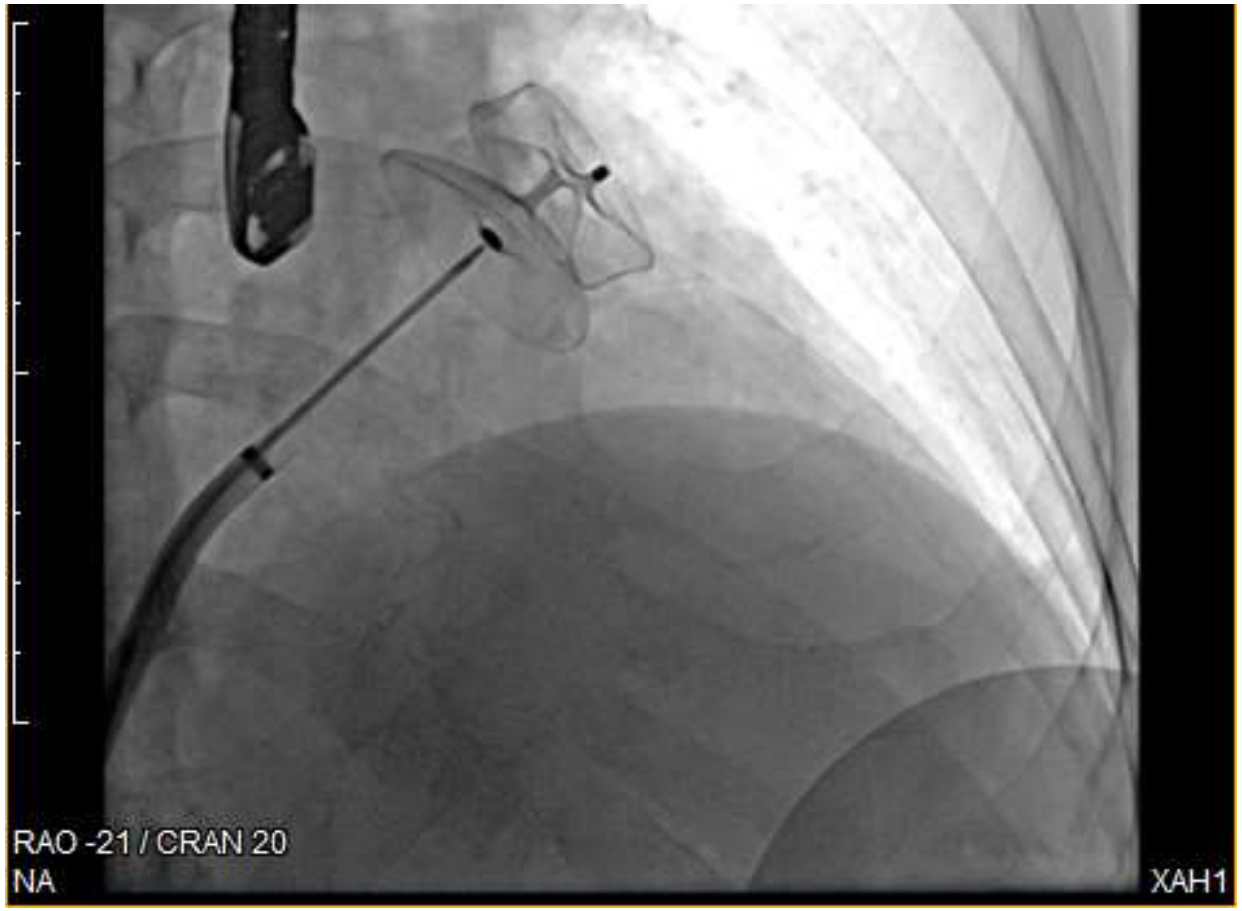
- 72/M
- H/O ischemic stroke
- Permanent AF
- Prior GI surgery
- Taking NOAC for SPAF
- Complaining dizziness
- Hb level of 6.9 mg/dL



- Stop NOAC
- Restart half-dose NOAC at day 5
- Sudden aphasia at day 14

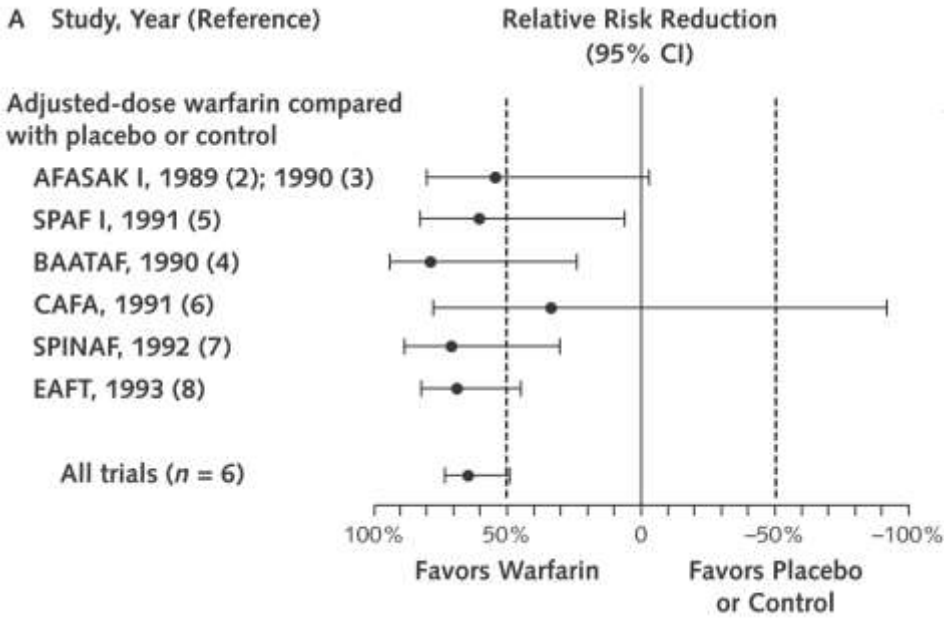


Case



- Successful LAAO + low dose NOAC

Oral anticoagulant for SPAF

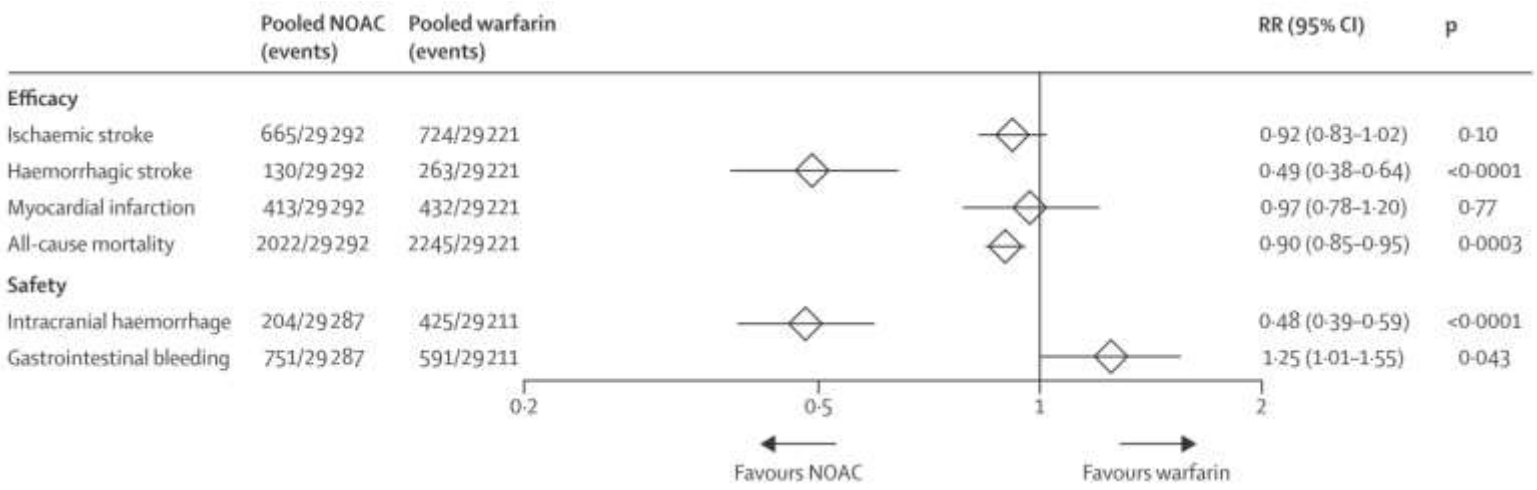


Warfarin
62% risk reduction

Ann Intern Med. 2007;146:857

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Christian T Ruff, Robert P Giugliano, Eugene Braunwald, Elaine B Hoffman, Naveen Deenadayalu, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takeshi Yamashita, Elliott M Antman



Lancet 2014; 383: 955

- OAC is a fundamental treatment for stroke prevention.
- Better efficacy and safety of NOAC was already proven in pivotal trials

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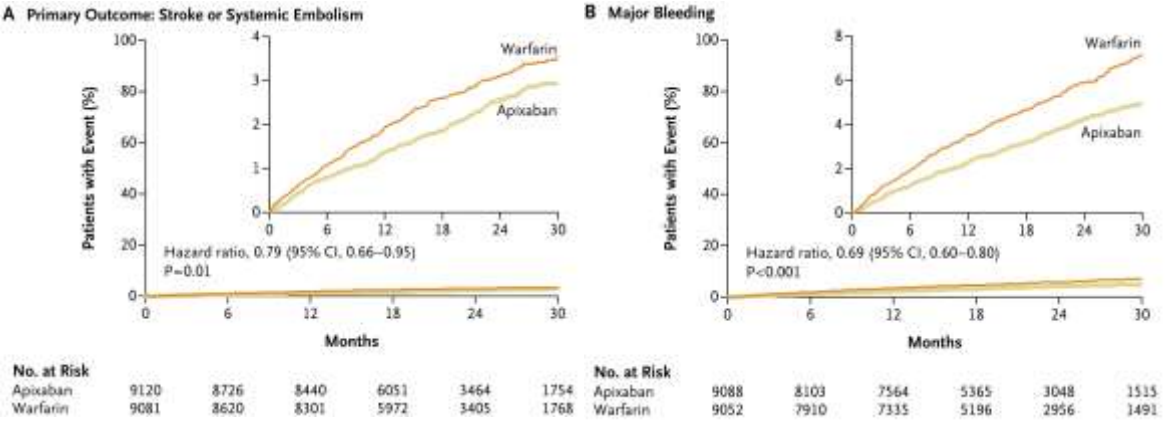
SPAF in AF: Pitfalls

- Obstacles to long-term OAC therapy
  - Bleeding
  - Non-compliance
  - Drug interaction
  - Side effects
  - Concerns in the elderly
  - Limited use in CKD
  - Residual stroke risk (2-5% / year)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation



Exclusion criteria

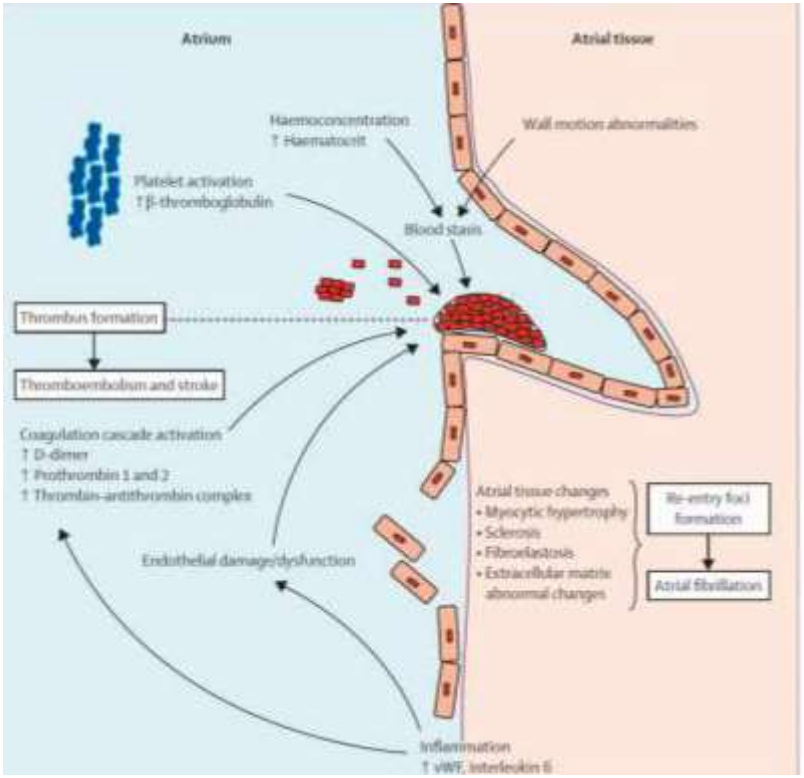
AF or atrial flutter due to reversible causes (eg, thyrotoxicosis, pericarditis)
Clinically significant (moderate or severe) mitral stenosis
Increased bleeding risk believed to be a contraindication to oral anticoagulation (eg, previous intracranial hemorrhage)
Conditions other than AF that require chronic anticoagulation (eg, prosthetic mechanical heart valve)
Persistent uncontrolled hypertension (SBP >180 mm Hg or DBP >100 mm Hg)
Active infective endocarditis
Planned major surgery
Planned AF or atrial flutter ablation procedure
Use of unapproved investigational drug or device in past 30 d
Required aspirin >165 mg/d
Simultaneous treatment with both aspirin and a thienopyridine (eg, clopidogrel, ticlopidine)
Severe comorbid condition with life expectancy ≤1 y
Active alcohol or drug abuse or psychosocial reasons that make study participation impractical
Recent stroke (within 7 d)
Severe renal insufficiency (serum creatinine level >2.5 mg/dL or calculated creatinine clearance <25 mL/min)
ALT or AST >2 × ULN or a total bilirubin ≥1.5 × ULN (unless an alternative causative factor [eg, Gilbert's syndrome] is identified)
Platelet count ≤100,000/mm^3
Hemoglobin level <9 g/dL
Inability to comply with INR monitoring

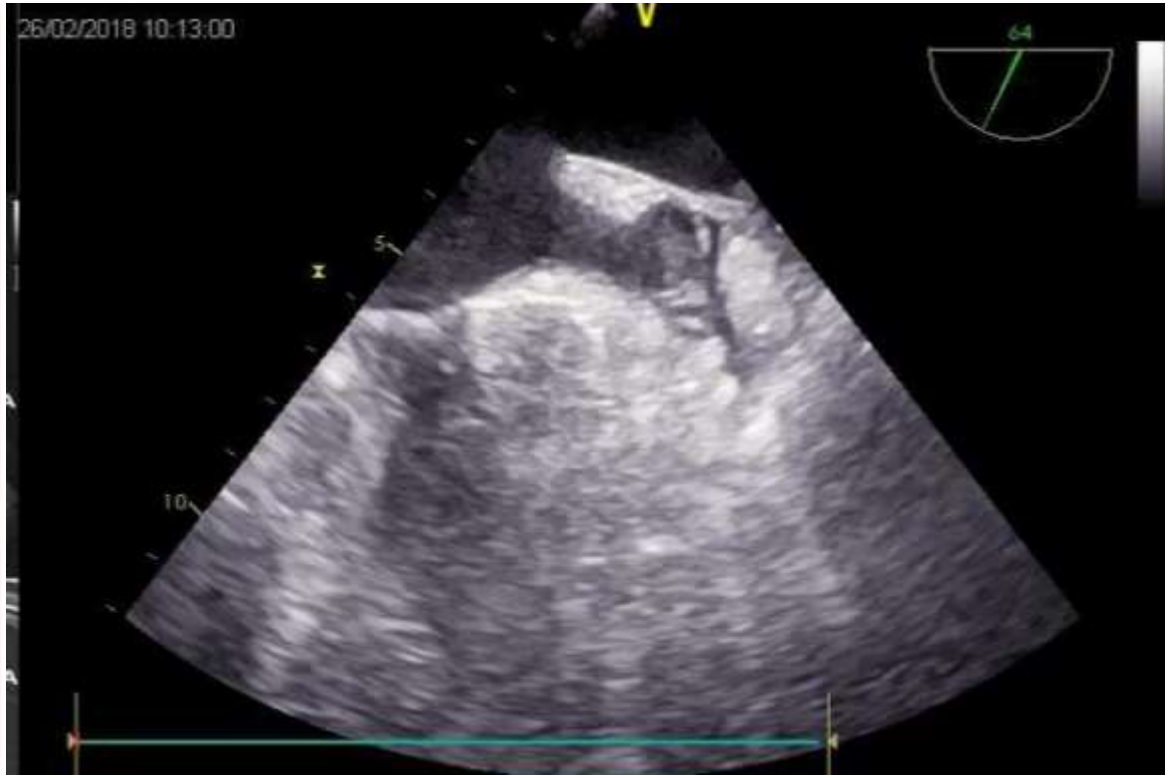
In RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE studies patients who had intolerance to VKA were usually excluded.

Rationale for LAA closure

- Absence of a solution for patients intolerant or refractory to OAC
- 10-20% of patients in NOAC studies gave it up
- Residual risk after NOAC (3-4%/year)

Thrombus formation





- Stasis in the LAA
- 90% of strokes in patients with NVAF can be attributed to formation of thrombi in the LAA

Evidence for LAA occlusion

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 3, 2021 VOL. 384 NO. 22

Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke

Variable	Occlusion (N=2379)	No Occlusion (N=2391)
Left atrial appendage occlusion‡		
Occlusion attempted — no. (%)	2131 (89.6)	NA
Occlusion method — no./total no. (%)§		
Cut and sew	939/1685 (55.7)	NA
Stapler	189/1685 (11.2)	NA
Closure device	255/1685 (15.1)	NA
Closure from within	233/1685 (13.8)	NA
Other approved techniques	69/1685 (4.1)	NA
Cardiac surgery		
Surgical procedure performed — no. (%)		
Isolated CABG	482 (20.3)	522 (21.8)
Isolated valve replacement	552 (23.2)	572 (23.9)
Other	1344 (56.5)	1296 (54.2)
Any valve procedure	1565 (65.8)	1614 (67.5)
Mitral	856 (36.0)	880 (36.8)
Aortic	837 (35.2)	858 (35.9)
Tricuspid	397 (16.7)	427 (17.9)
Pulmonic	2 (0.1)	4 (0.2)
Any aortic procedure	146 (6.1)	134 (5.6)
Concomitant surgical ablation of atrial fibrillation — no. (%)	809 (34.0)	753 (31.5)
Received assigned procedure — no. (%)	2131 (89.6)	2262 (94.6)

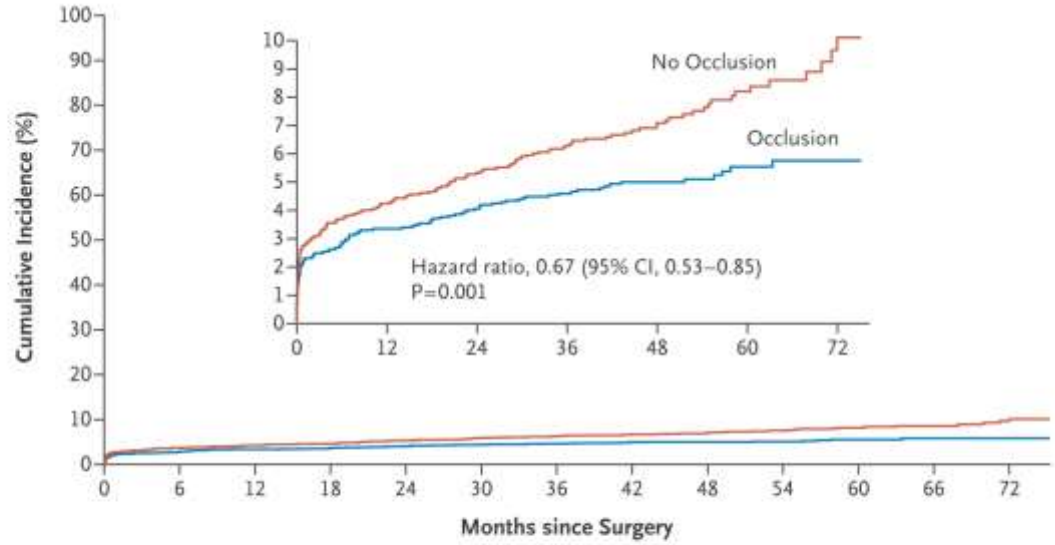


Figure 1. Cumulative Incidence of Stroke or Systemic Arterial Embolism.

The participants in the occlusion group underwent left atrial appendage occlusion at the time of cardiac surgery for another indication, and those in the no-occlusion did not undergo left atrial appendage occlusion at the time of cardiac surgery; all participants were expected to receive usual care. The inset shows the same data on an enlarged y axis.

- LAAO lower the risk of stroke or systemic embolism in patients with AF underwent cardiac surgery

N Engl J Med 2021; 384:2081

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Current guideline on LAAO

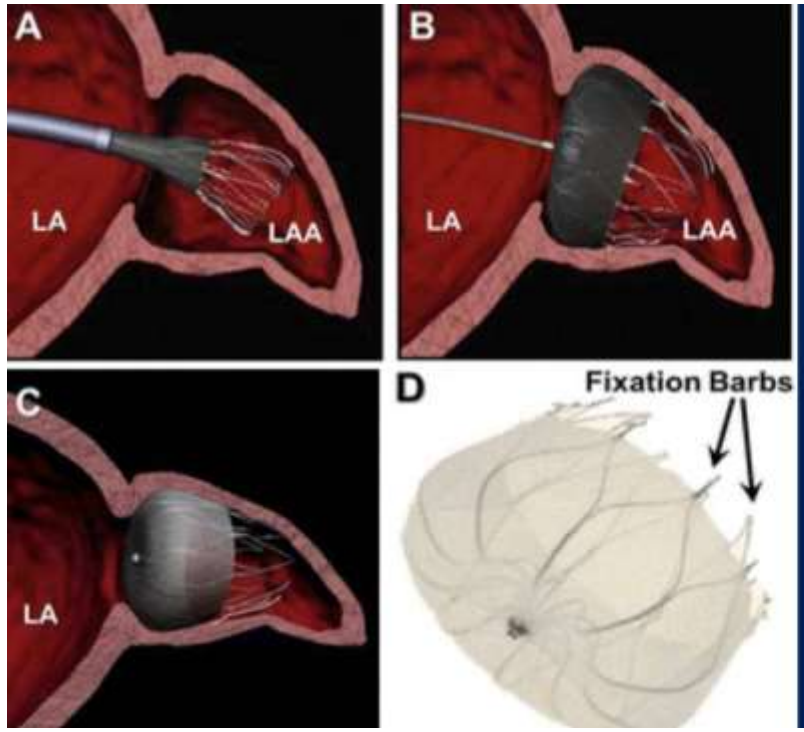
AHA/ACC 2019

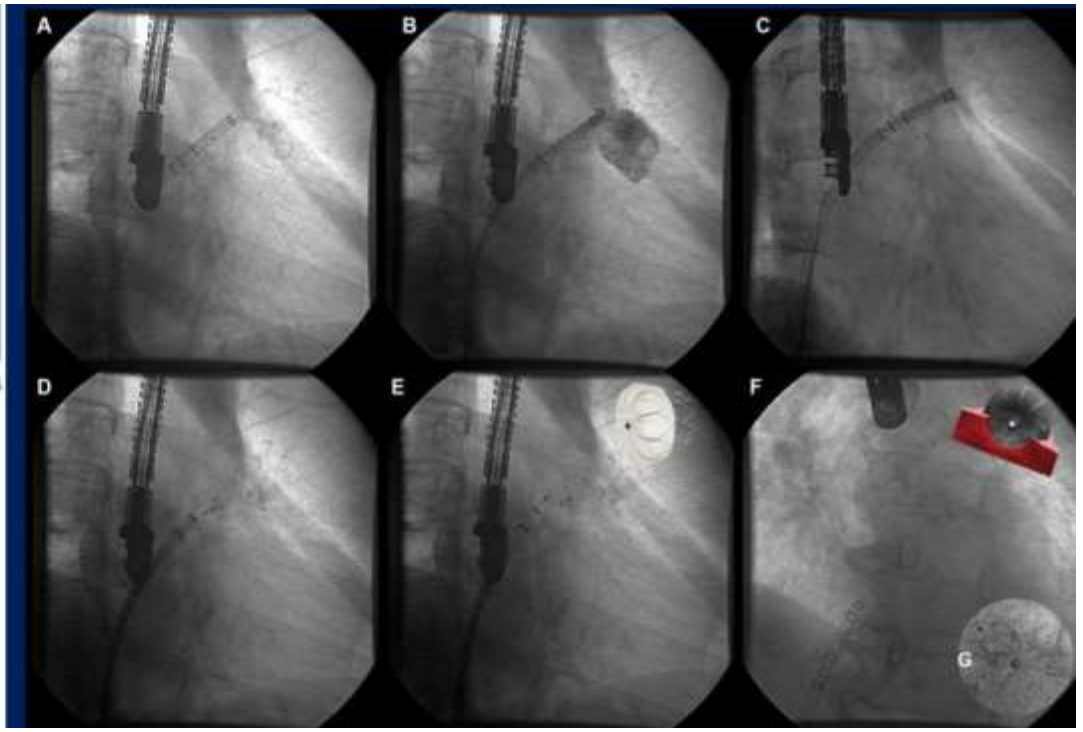
Recommendation for Percutaneous Approaches to Occlude the LAA Referenced studies that support the new recommendation are summarized in Online Data Supplement 4.		
COR	**LOE**	**Recommendation**
IIb	B-NR	1. Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation.[S4.4.1-1–S4.4.1-5] **NEW:** Clinical trial data and FDA approval of the Watchman device necessitated this recommendation.

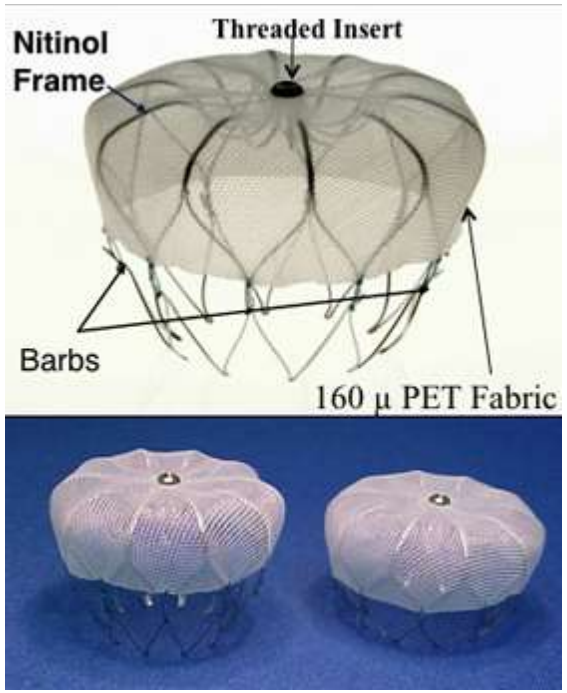
ESC 2020

Recommendations for occlusion or exclusion of the LAA		
LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g. intracranial bleeding without a reversible cause).[448,449,481,482]	IIb	B
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.[459,483]	IIb	C

LAA occlusion devices (1) - Watchman







- A catheter-delivered heart implant designed to close the left atrial appendage
- Permanently implanted at or slightly distal to the ostium of the LAA

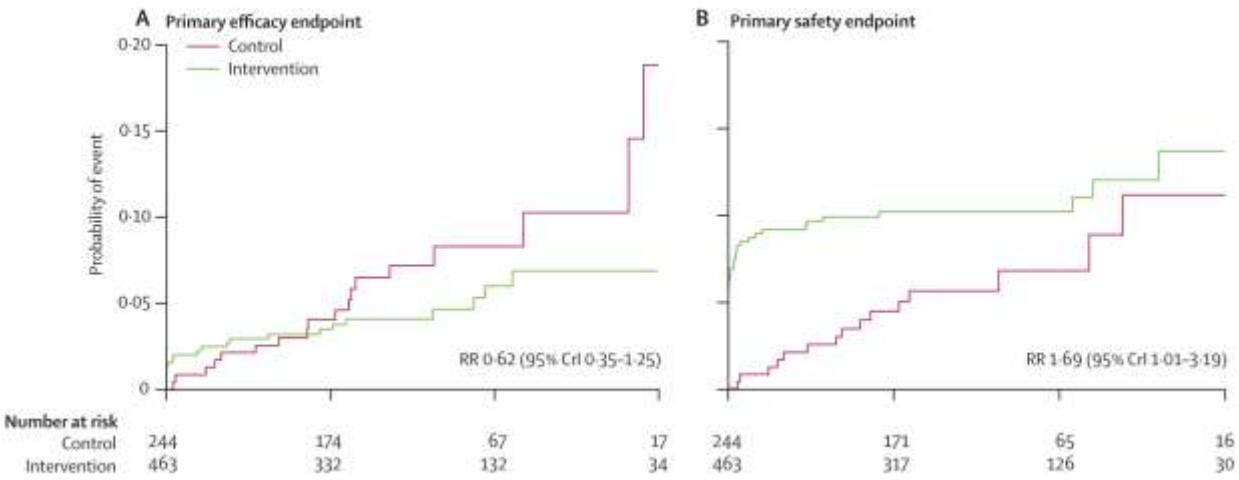
Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial

CHADS2 score > 1 + NVAF

LAA
N = 463

Warfarin
N = 244

Efficacy : Stroke, SE, CV death
Safety: Major or procedure related bleeding



- Efficacy of LAAO is non-inferior to warfarin
- Most safety events were periprocedural complication
- LAAO provide an alternative strategy to warfarin for SPAF

Lancet 2009;374:534

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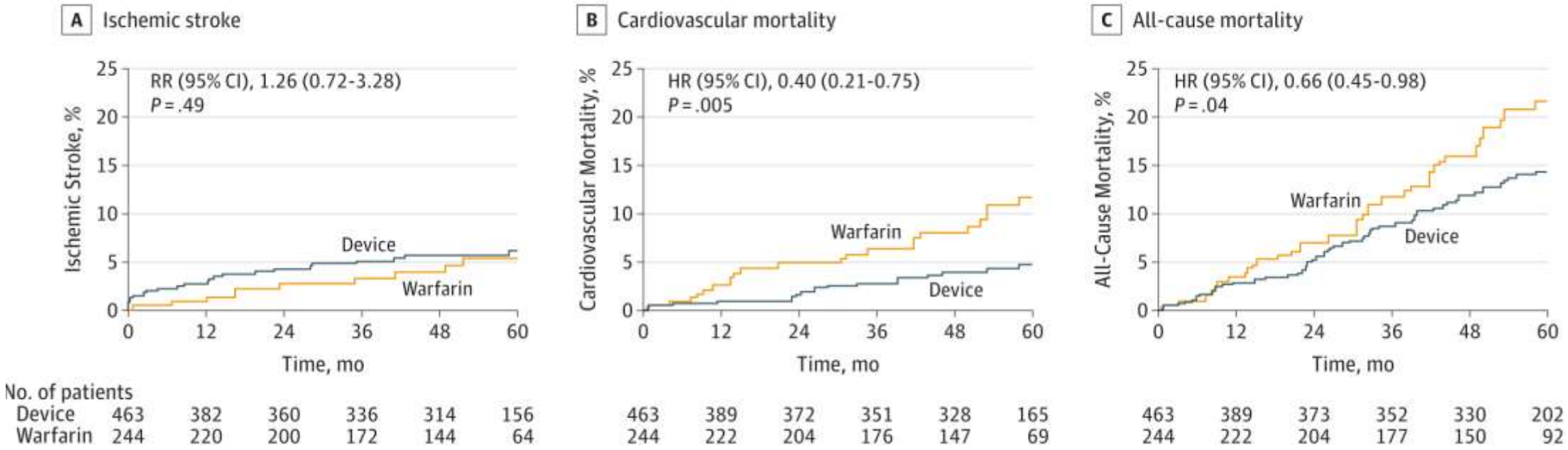
Original Investigation

Percutaneous Left Atrial Appendage Closure vs Warfarin for Atrial Fibrillation

A Randomized Clinical Trial

Vivek Y. Reddy, MD; Horst Sievert, MD; Jonathan Halperin, MD; Shephal K. Doshi, MD; Maurice Buchbinder, MD; Petr Neuzil, MD, PhD; Kenneth Huber, MD; Brian Whisenant, MD; Saibal Kar, MD; Vijay Swarup, MD; Nicole Gordon, BSEE; David Holmes, MD; for the PROTECT AF Steering Committee and Investigators



- Non-inferior in stroke or SE; Superior in mortality

JAMA 2014;312:1988

Clinical evidence (Watchman)

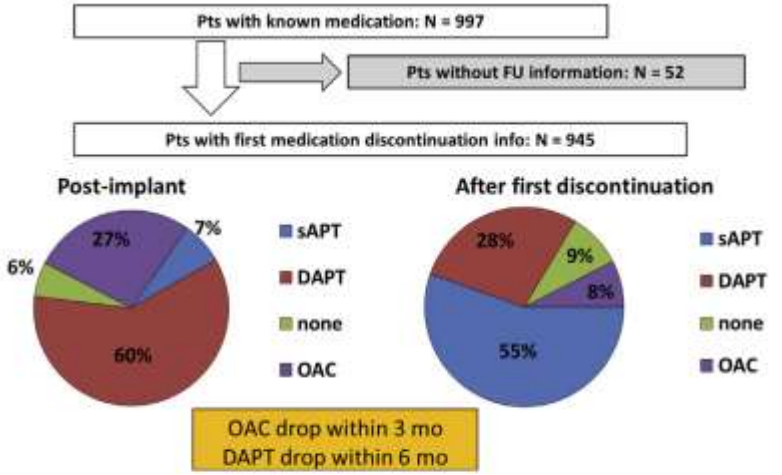


Figure 2 Flowchart of anti-coagulation drugs used after WATCHMAN implant throughout 1-year follow-up. DAPT = dual antiplatelet therapy; FU = follow-up; OAC = oral anticoagulation; Pts = patients; sAPT = single antiplatelet therapy.

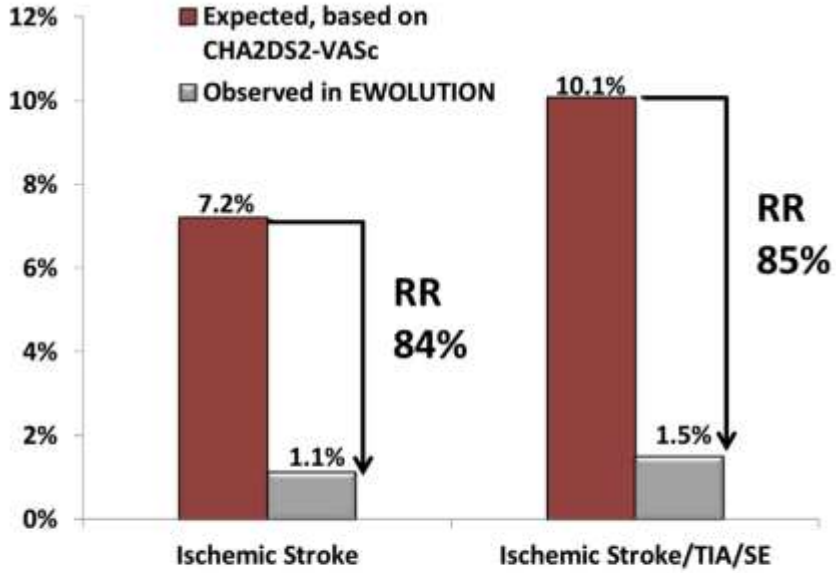


Figure 3 Actual stroke rate, and calculated stroke risk based o CHA_2DS_2-VASc score, and the relative risk reduction for the total EWOLU TION patient cohort after 1-year follow-up. RR = relative risk; SE = sys emic embolism; TIA = transient ischemic attack.

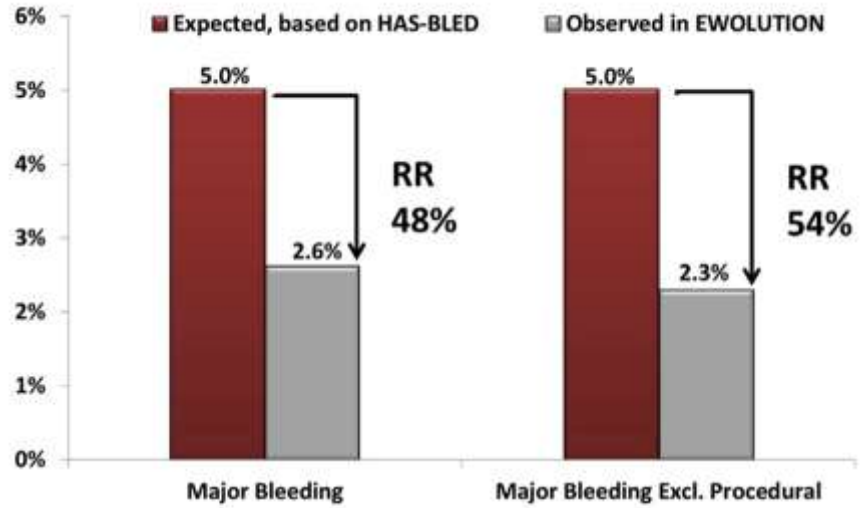


Figure 4 Actual major bleeding rate excluding procedural bleeding events, and calculated major bleeding risk based on HAS-BLED score, and the relative risk reduction for the total EWOLUTION patient cohort after 1-year follow-up. RR = relative risk; SE = systemic embolism; TIA = transient ischemic attack.

- EWOLUTION registry
- Procedure success rate of 98.5%
- Better efficacy and safety outcomes in real-world setting

Heart rhythm 2017;14:1302

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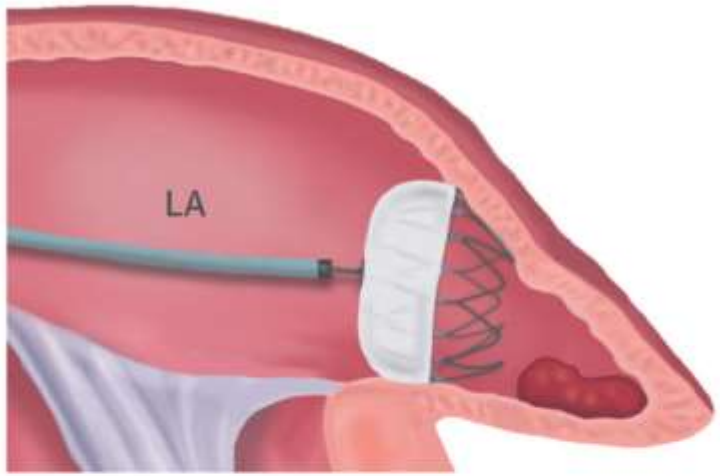
Clinical evidence (Watchman)

Study	Post-procedural medication	Study design	Mean follow-up	Success rate	MAE	Annual Stroke/SE risk vs. control	Annual bleed risk vs. control	Death (%)
PROTECT AF[17-19] *n* = 707, 2014	Aspirin indefinitely, Warfarin 45 days, Clopidogrel 4.5 months	RCT vs. warfarin	3.8 years	90.9%	3.6 vs. 3.1 per 100 patient-years	2.5% vs. 3.8%	4.8% vs. 7.4%	3.7% vs. 9.0%
PREVAIL[20] *n* = 407, 2014	Aspirin indefinitely, Warfarin 45 days, Clopidogrel 4.5 months	RCT vs. warfarin	18 months	95.1%	4.2% vs. 8.7% in PROTECT AF	2.3% vs. 0.7%	–	2.6% vs. 2.2%
CAP[21] *n* = 460, 2011	Aspirin indefinitely, Warfarin 45 days, Clopidogrel 4.5 months	Registry, multi-centre	12 months	95.0%	4.1% vs. 8.7% in PROTECT AF	–	–	–
ASAP[22] *n* = 150, 2013	Aspirin indefinitely Clopidogrel 6 mo	Registry, multi-centre	14 months	94.7%	8.7%	1.7% vs. 7.3%	–	5.0%
EWOLUTION[23] *n* = 1021, 2016	Warfarin 45 days (27%), aspirin and Clopidogrel for 6 months (59%), aspirin only (7%), none (6%)	Registry, multi-centre	30 days	98.5%	2.7% vs. 8.6% in PROTECT AF	–	–	0.7%

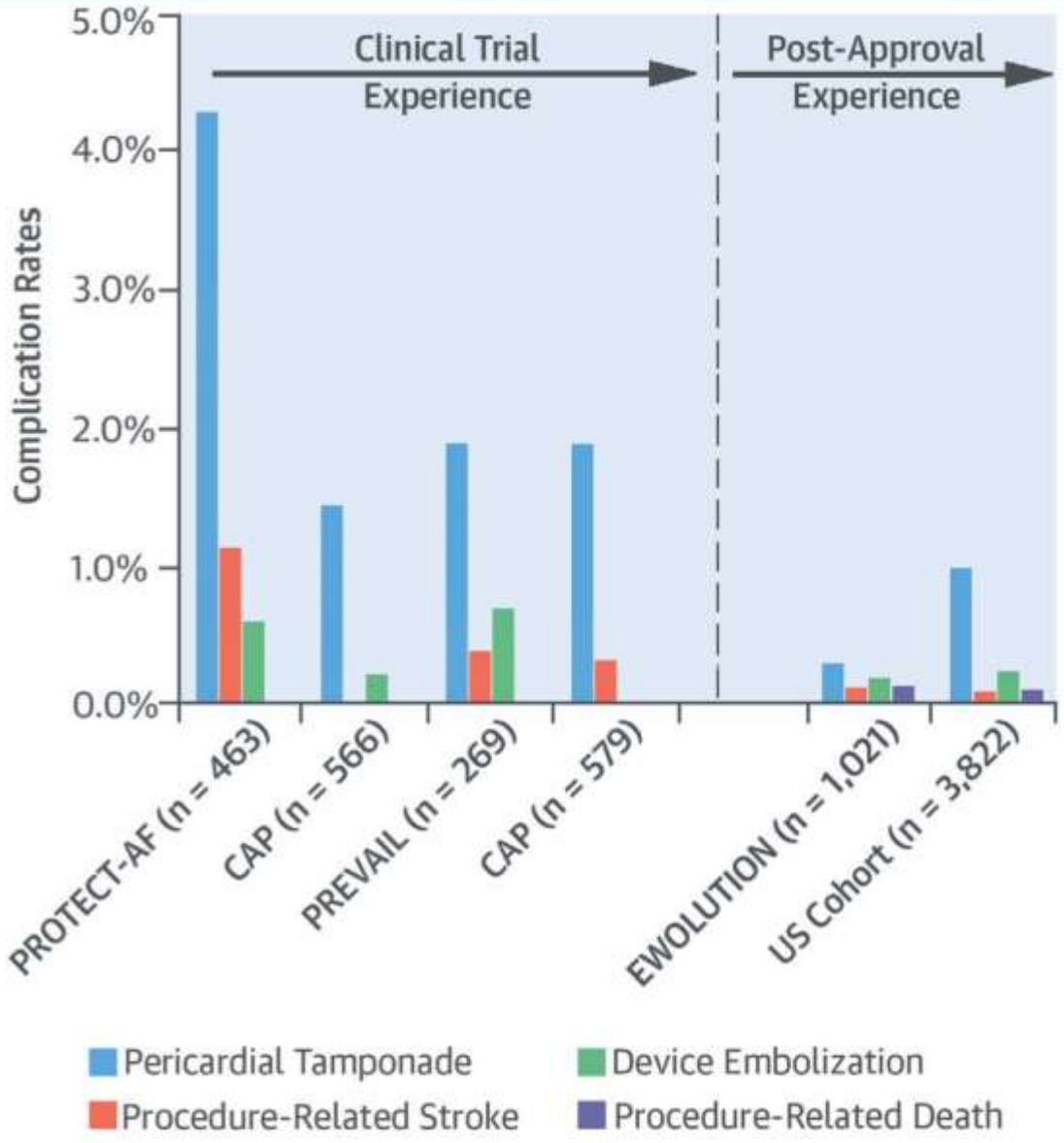
Coloured cells indicate studies that included subjects with contraindication to anticoagulation.
DAPT, dual antiplatelet therapy; MAE, major adverse events; SE, systemic embolism.[24]

Europace 2018;20:1412

Major Complication Rates Across Watchman Clinical Studies

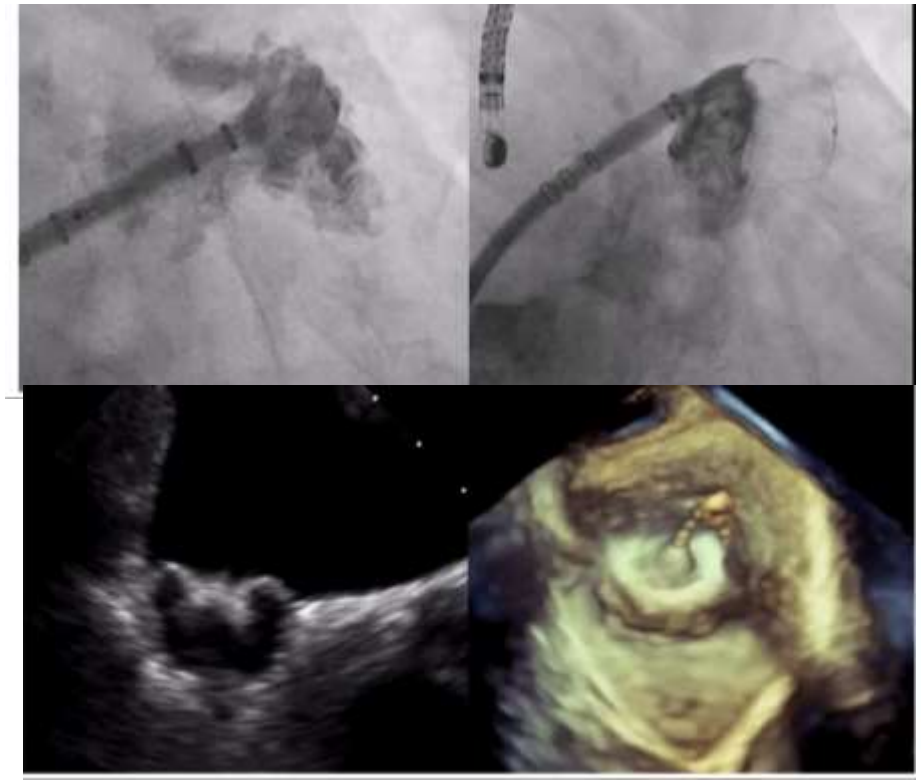


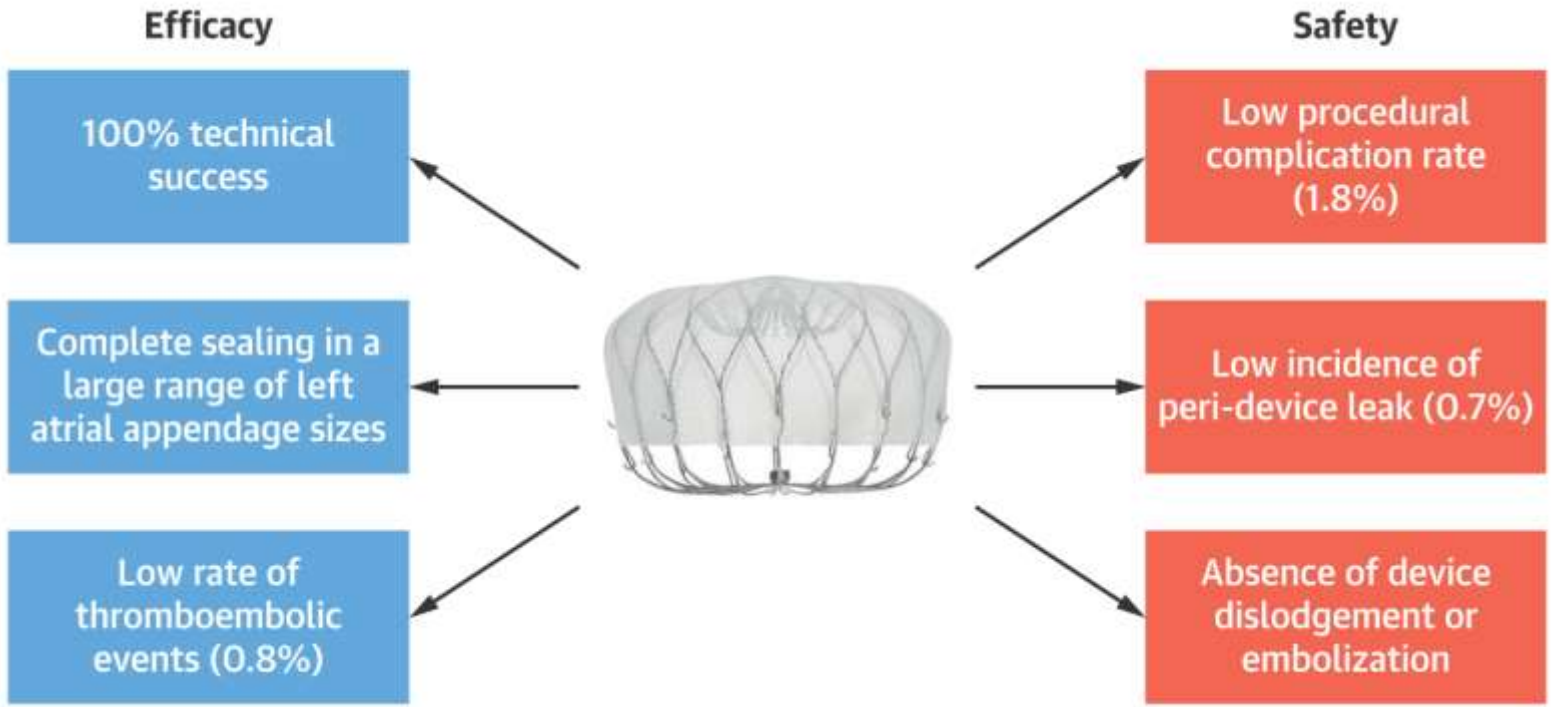
Procedural Parameters	Aggregate Clinical Data
Number of Procedures	6,720
Implantation Success, %	94.9%
Complication Rates	
Pericardial Tamponade	1.24%
Procedure-Related Stroke	0.18%
Device Embolization	0.25%
Procedure-Related Death	0.06%



JACC 2017:69:253

Newer generation watchman - FLEX

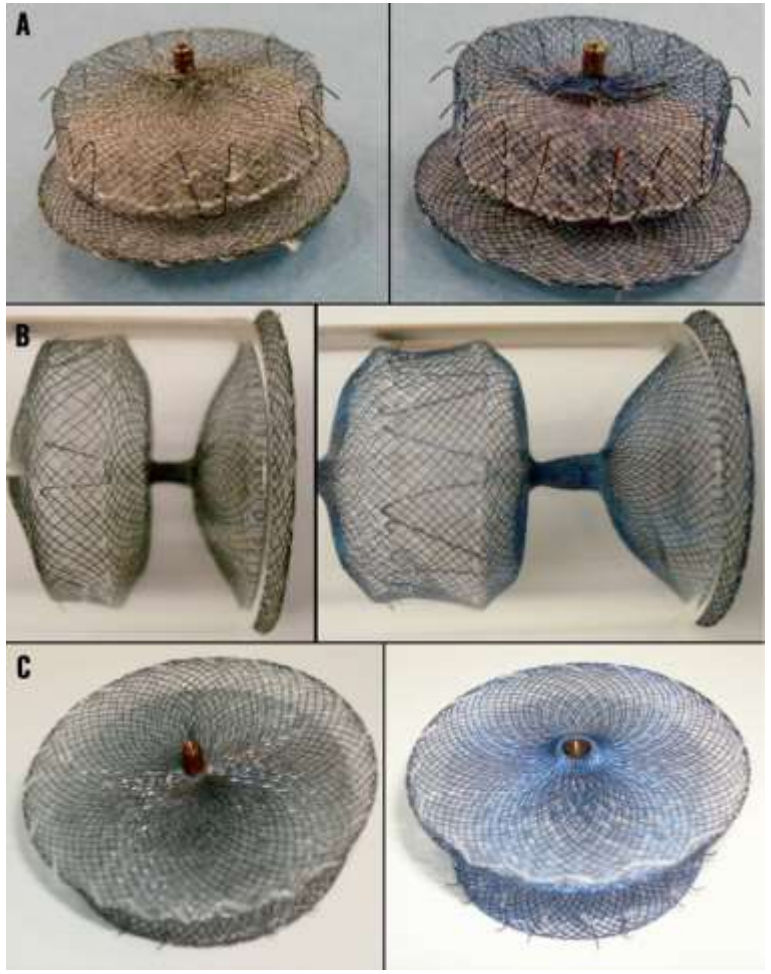


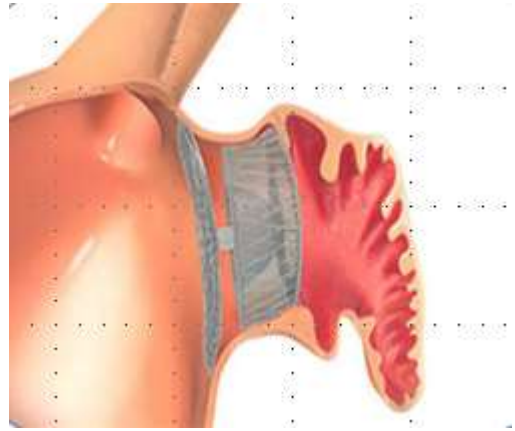


J Am Coll Cardiol Intv. 2020;13(23):2732

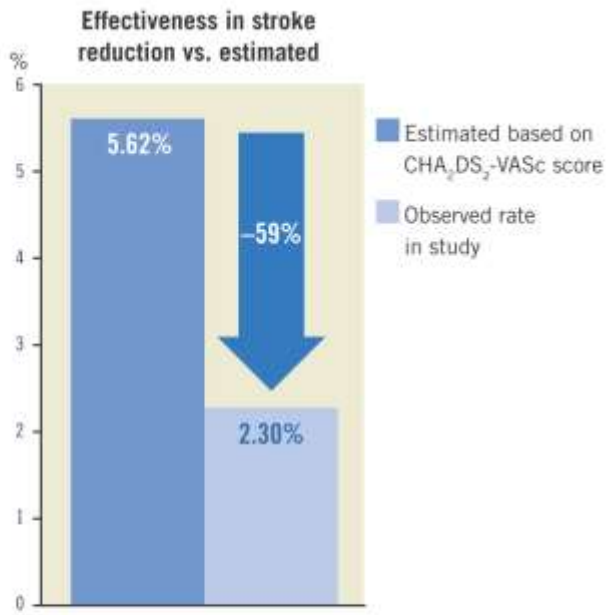
LAA occlusion devices (2) - Amulet

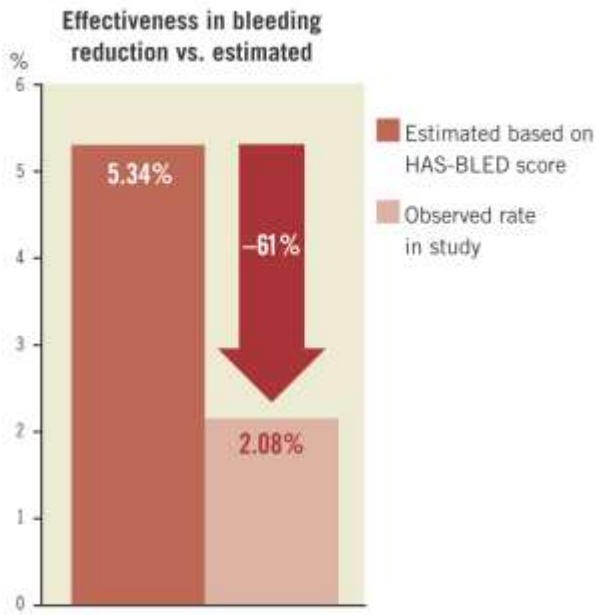
- Easy to use
- Retrievable – repositionable
- Proximal implant at LAA neck
- Increasing stability
- Complete closure with large lobe
- Lesser device thrombosis





Clinical evidence (Amulet)





Total patients	Total patient-years	CHA_2DS_2-VASc score
1,001	1,349	4.43

Estimated stroke rate per CHA_2DS_2-VASc	Actual annual stroke rate (No. strokes+TIA)
5.62%	2.30% (31)

Total patients	Total patient-years	HAS-BLED score
1,001	1,349	3.12

Estimated bleeding rate per HAS-BLED	Actual annual bleeding rate (No. major bleeds)
5.34%	2.08% (28)

- Multicenter registry including 1,047 patients in Europe
- ACP showed favorable outcome for prevention of AF related thromboembolism

Eurointervention 2015

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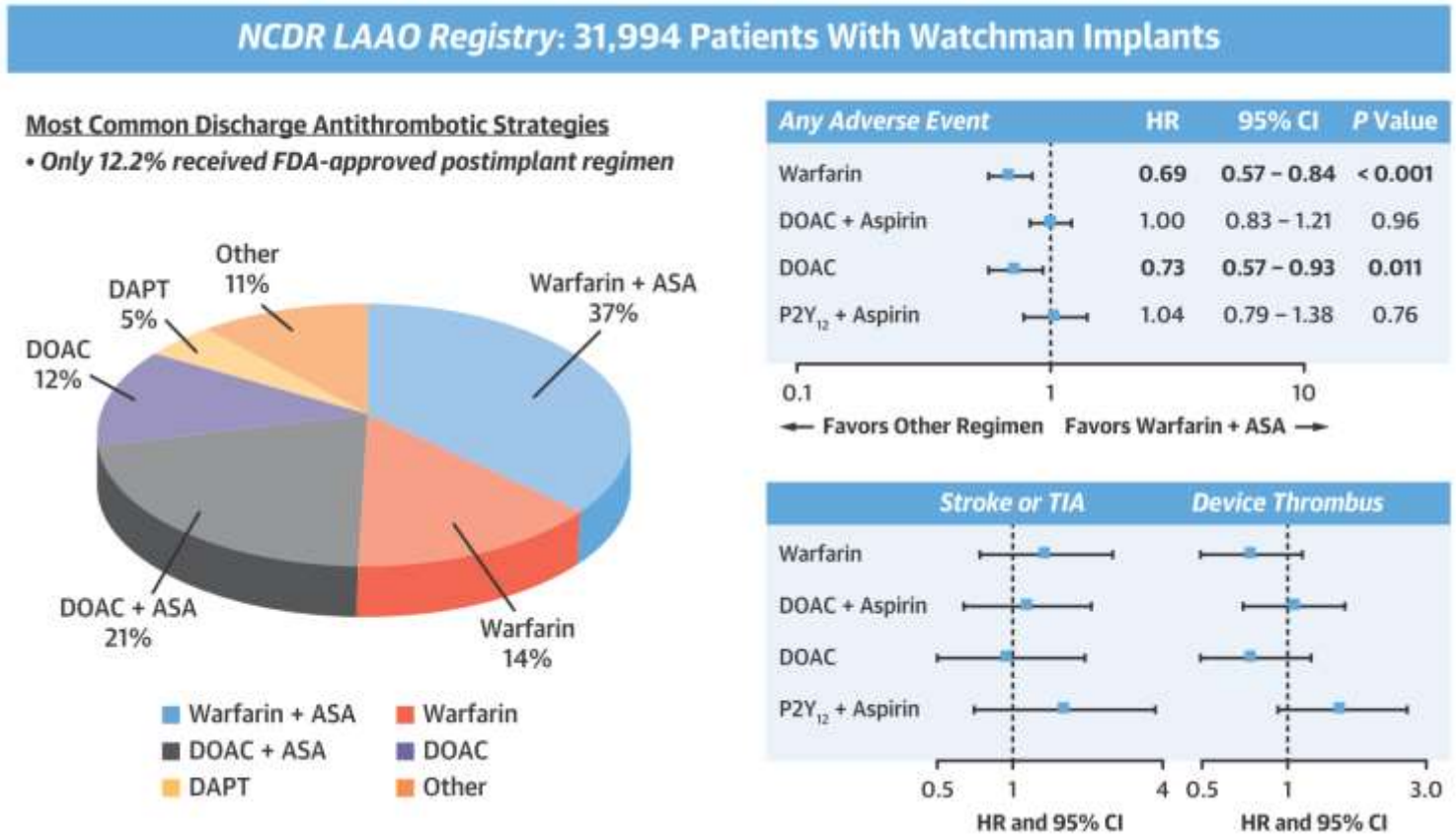
Clinical evidence (Amulet)

Table 2 Amplatzer Cardiac Plug and Amulet studies

Study	Post-procedural medication	Study design	Mean follow-up	Success rate	MAE	Annual Stroke/SE risk vs. control	Annual bleed risk vs. control	Death %
Urena *et al.*[27] $n = 52$	1–3 months DAPT, life-long aspirin	Registry, multi-centre	20 months	98.1%	5.8%	3.4% vs. 10.0%	3.4% vs. 8.7%	5.8
Kefer *et al.*[28] $n = 90$	1 month DAPT, life-long aspirin	Registry, multi-centre	1 year	95.0%	12.0%	2.1% vs. 5.1%	0% vs. –	5.6
Lopez-Minguez *et al.*[29] $n = 167$	3 months DAPT, 3 months aspirin	Registry, multi-centre	24 months	94.6%	5.4%	2.4% vs. 8.3%	3.1% vs. 6.6%	10.8
Santoro *et al.*[30] $n = 134$	Variable	Registry	680 days	93.3%	2.2% procedural complication	2.5% vs. 7.7%	1.3% vs. 3.1%	6.0
Tzikas *et al.*[31] $n = 1047$	1–3 month DAPT, > 3 months of aspirin	Registry, multi-centre	13 months	97.3%	5.0%	2.3% vs. 5.6%	2.1% vs. 5.3%	4.2

Coloured cells indicate studies that included subjects with contraindication to anticoagulation.
DAPT, dual antiplatelet therapy; MAE, major adverse events; SE, systemic embolism.

Post-procedure antithrombotic therapy

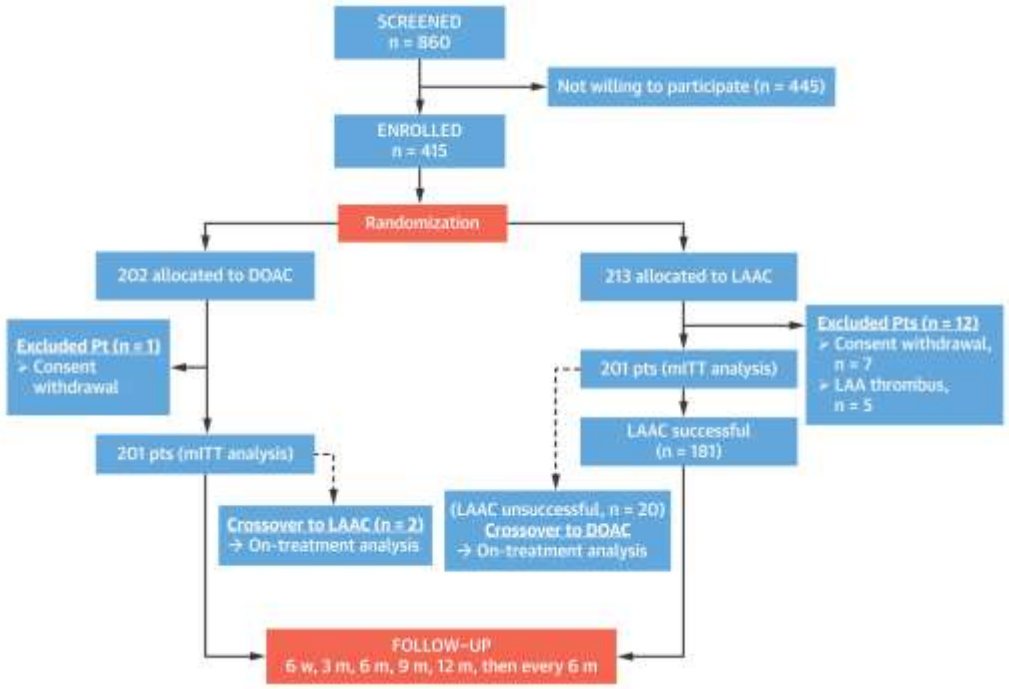


- OACs are more frequently used in US practice
- Optimal antithrombotic strategy after LAAO should be settled

J Am Coll Cardiol. 2022;79(18):1785

Data in NOAC era

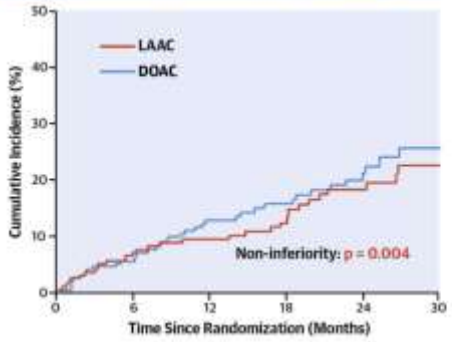
Left Atrial Appendage Closure Versus Direct Oral Anticoagulants in High-Risk Patients With Atrial Fibrillation



PRAGUE-17 Randomized Clinical Trial

- 402 High-Risk AF Pts ➡ Randomized
  - CHA_2DS_2-VASc = 4.7 ± 1.5
  - HAS-BLED = 3.1 ± 0.9
- Follow-up: 20.8 ± 10.8 mo (695 pt-year)

Primary Endpoint
Stroke, TIA, SE, CV Death, Bleeding, or Complications



	sHR (95% CI)	p value
Primary Endpoint		
mITT	0.84 (0.53-1.31)	0.44
Per Protocol	0.82 (0.52-1.30)	0.40
On-Treatment	0.79 (0.49-1.25)	0.31
All-Stroke/TIA	1.00 (0.40-2.51)	0.99
CV Death	0.75 (0.34-1.62)	0.46
Major + NMCR Bleeding		
All	0.81 (0.44-1.52)	0.51
Nonprocedural	0.53 (0.26-1.06)	0.07

- In patients with high risk of bleeding and non-valvular AF, LAAC was non-inferior to NOAC in preventing stroke/death/bleeding/complications.

J Am Coll Cardiol 2020;75:3122

Ongoing trials

CHAMPION-AF

Primary Endpoints:

- WATCHMAN FLX is non-inferior for the occurrence of stroke (including ischemic and/or hemorrhagic), cardiovascular (CV) death (including hemorrhagic and/or unexplained death), and systemic embolism at 36 months.
- WATCHMAN FLX is superior for non-procedural bleeding (ISTH major bleeding and clinically relevant non-major bleeding) at 36 months.
- WATCHMAN FLX is non-inferior for the occurrence of ischemic stroke and systemic embolism at 60 months.

CATALYST

Study Design Go to

Study Type:	Interventional (Clinical Trial)
Estimated Enrollment:	2650 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Single (Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	Clinical Trial of Atrial Fibrillation Patients Comparing Left Atrial Appendage Occlusion Therapy to Non-vitamin K Antagonist Oral Anticoagulants
Actual Study Start Date:	July 7, 2020
Estimated Primary Completion Date:	December 2024
Estimated Study Completion Date:	April 2029

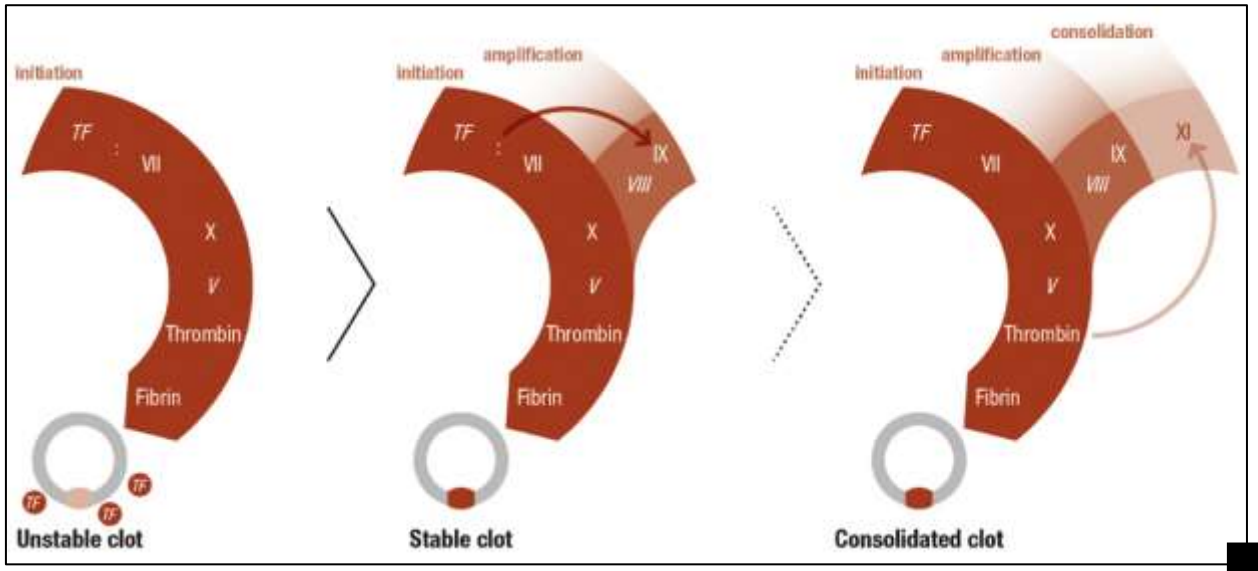
Resource links provided by the National Library of Medicine NIH NLM

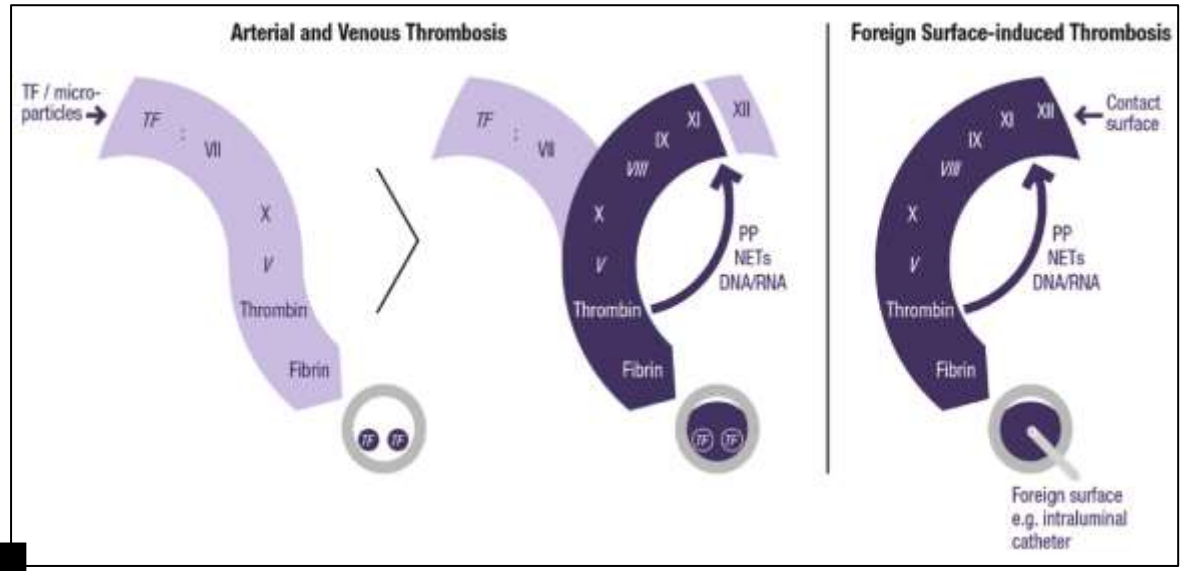
MedlinePlus Genetics related topics: Familial atrial fibrillation

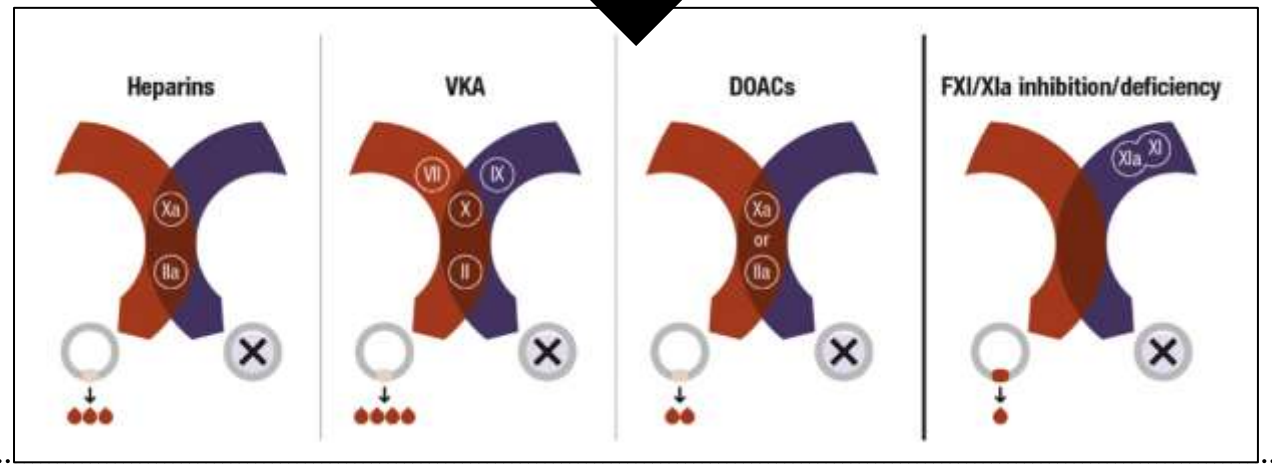
MedlinePlus related topics: Atrial Fibrillation

U.S. FDA Resources

FXI inhibitor : thrombosis – hemostasis uncoupling







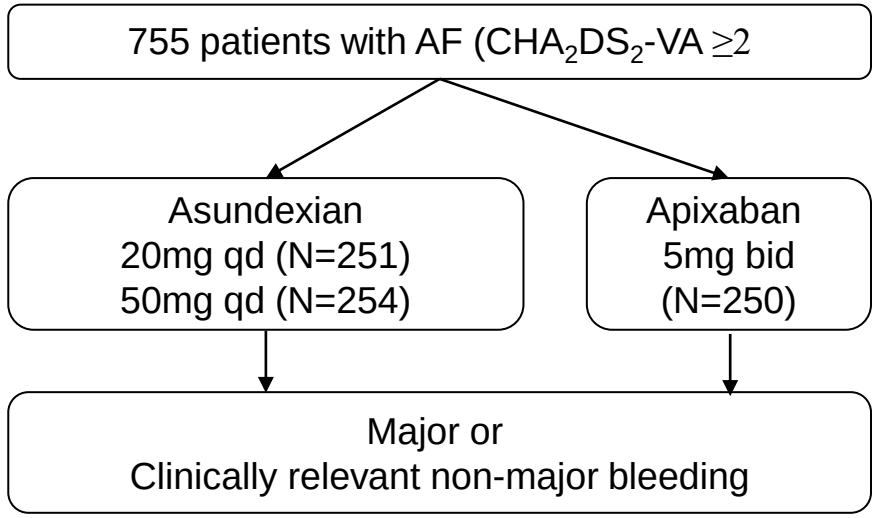
J Am Coll Cardiol 2021;78:625

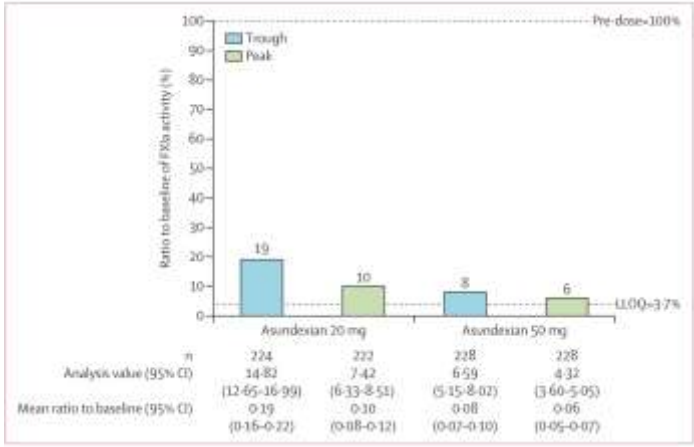
서울아산병원 Asan Medical Center

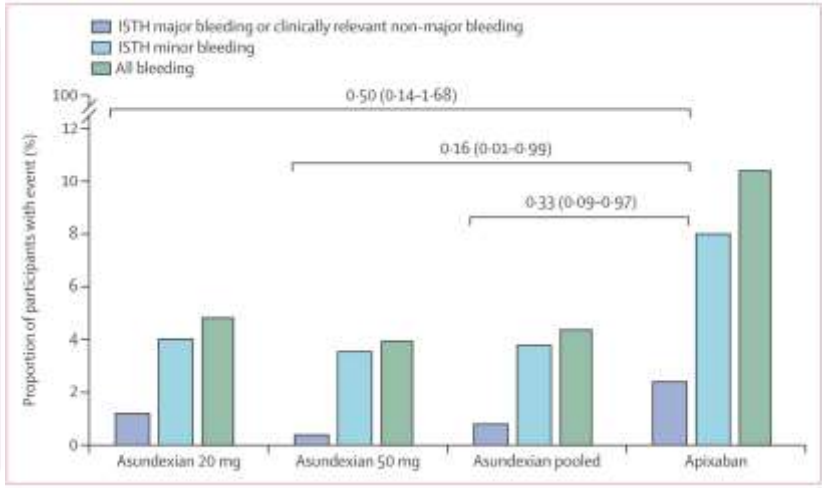
울산대학교

PACIFIC AF

Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study







- FXI activity was reduced >80% (20mg) or >90% (50mg)
- During 4 weeks, risk of bleeding was decreased compared to apixaban
- Number of bleeding was half of that anticipated (N=10, 3:1:6)
- Cannot assess the efficacy against thrombosis

Lancet 2022; 399: 1383

Future perspective

- Larger trial data on LAAO vs. NOAC or LAAO vs. FXI inhibitor
- Optimal post-procedural antithrombotic therapy
  - Antiplatelet vs. low-dose NOAC
- Data on newer generation LAAO
- Optimal delivery method
  - TEE vs. ICE vs. fluoroscopy
- LAAO in structural heart disease

Summary

- LAAO is a reasonable alternative to OAC in AF patients
- New data comparing LAAO with newer OACs (NOACs or FXIa inhibitors) are required
- The optimal antithrombotic therapy after LAAO should be further evaluated.