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Left Atrial Appendage Occlusion for Stroke Prevention in Nonvalvular Atrial Fibrillation

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MGH 1811 MASSACHUSETTS GENERAL HOSPITAL
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Objectives

- Summarize the challenges associated with stroke prevention for patients with AF.
- Describe the role of left atrial appendage (LAA) occlusion technology in stroke prevention.
- Summarize the patient outcomes associated with the use of LAA occlusion devices.

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AF: Scope of the Problem

Today

- AF is the most common sustained arrhythmia in adults.
- 33.5 million people affected worldwide in 2010.[1]

Tomorrow

- AF is a growing epidemic in developed and developing countries.
- The number of people affected by AF is expected to double by 2050.[2]

1. Chugh et al. 2014 Circulation 129: 837–847.
2. Ball et al. 2013 Int J Cardiol 167:1807–1824.

Consequences of AF

- Morbidity and mortality higher for patients with AF than for patients without AF.
- Worse outcomes in AF are driven by increase in stroke risk: AF increases risk of stroke by 500%.
- In the US, ~18% of patients presenting with stroke have AF.[3]

3. Alkhouli et al. 2018 JACC Clin EP 4:618–625.

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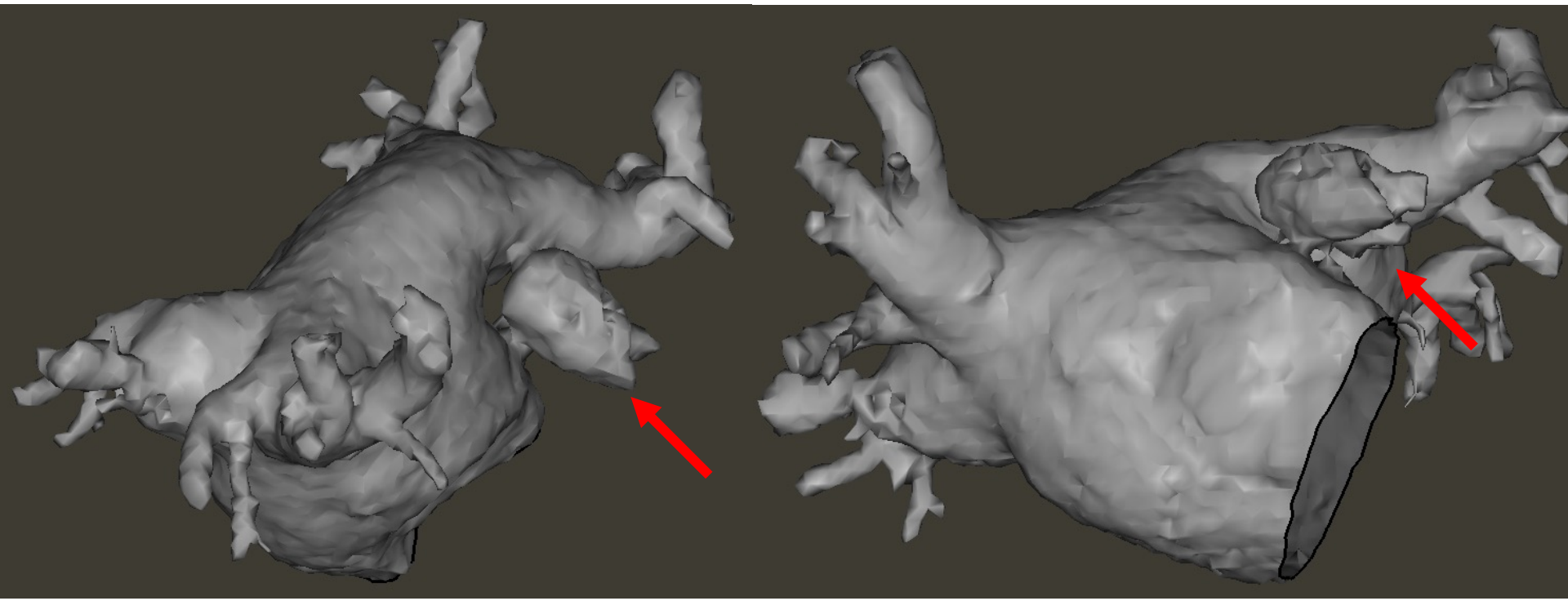
Pathophysiology of AF-Related Stroke



Sluggish blood flow in left atrial appendage leads to thrombus formation and embolization.[4]

4. Ptaszek LM et al. 2013 JICRM 4:1-5.

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Question 1

Which of the following is true regarding mortality rates of AF-related strokes:

1. Mortality of AF-related strokes is 30% higher than non-AF-related strokes.
2. Mortality of AF-related strokes is 40% higher than non-AF-related strokes.
3. Mortality of AF-related strokes is 50% higher than non-AF-related strokes.
4. Mortality of AF-related strokes is 60% higher than non-AF-related strokes.

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Question 2

Which of the following is true regarding permanent disability for AF-related strokes:

1. Permanent disability is observed for 30% of patients with AF-related stroke.
2. Permanent disability is observed for 40% of patients with AF-related stroke.
3. Permanent disability is observed for 50% of patients with AF-related stroke.
4. Permanent disability is observed for 60% of patients with AF-related stroke.

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Question 2

Which of the following is true regarding permanent disability for AF-related strokes:

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AF-Related Strokes are Associated with Worse Outcomes than Non-AF Strokes

- AF-related strokes are associated with higher acute morbidity and mortality.[5,6]
  - >50% increase in mortality as compared with strokes not due to AF (~20% to ~33%).
- 50% of patients with AF-related stroke experience permanent disability.
  - ~30% for patients with stroke not related to AF.

5. Lamassa et al. 2001 Stroke 32:392-398.
6. Steger et al. 2004 Eur Heart J 25:1734-1740.

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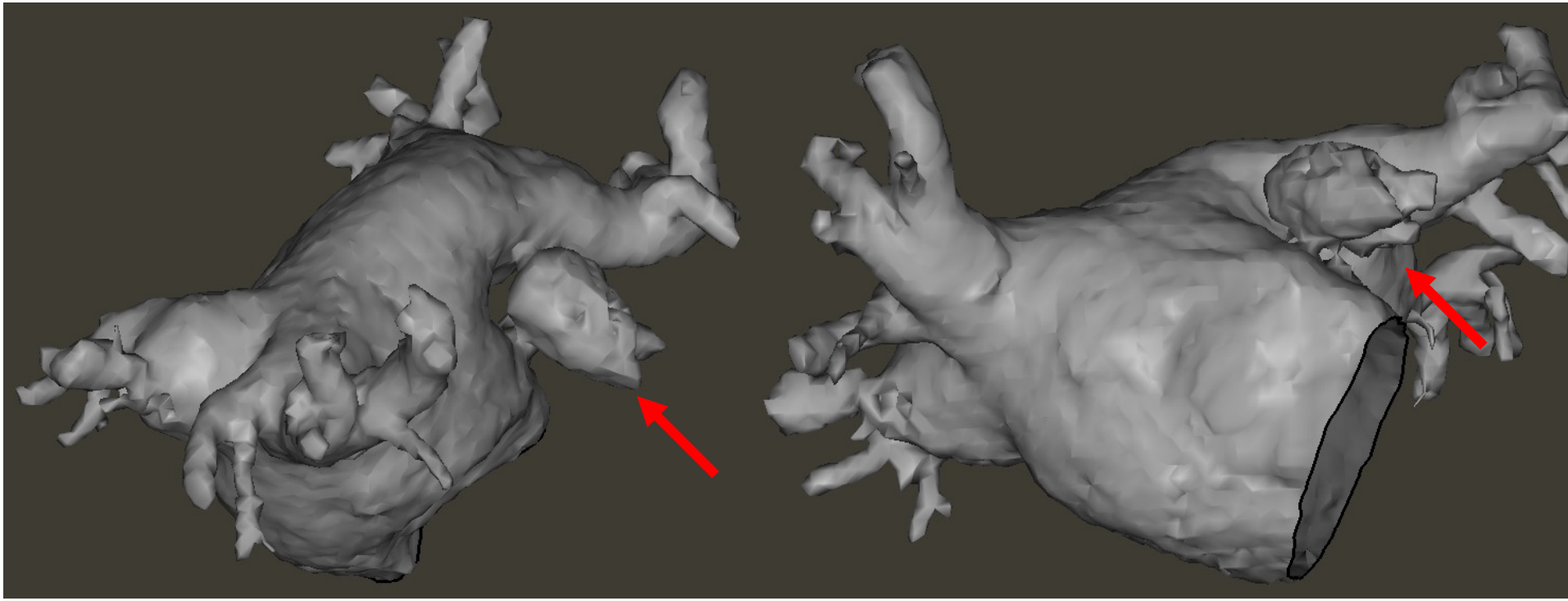
Worse Outcomes with AF-Related Stroke

Superior RAO



AF-related strokes:

- More likely to be bilateral / involve more tissue
- Hemorrhagic conversion increased
- Higher rate of recurrence

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Stroke Prevention in Non-Valvular AF

- Oral anticoagulant (OAC) therapy is the cornerstone of stroke risk reduction.[7]

- Appropriate use of OAC can reduce the risk of AF-related stroke by ~65%.

- Guidelines support the use of OAC for stroke risk reduction in qualifying patients with NVAF.[8,9]
  - Risk of AF-related stroke described by CHADS-VASC score

7. Alkhouli et al. 2018 JACC 71:2790-2801.
8. Kirchof et al. 2016 Eur Heart J 37:2893-2962.
9. January CT et al. 2019 JACC Epub ahead of print.

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Calculating Risk of NAVF-Related Stroke

CHADS-VASC score[10]

Congestive heart failure +1

HTN +1

Age ≥ 65 +1

Age ≥ 75 +1

Diabetes +1

Stroke/TIA/thromboembolism +2

Sex (female) +1

Vascular disease (peripheral or CAD) +1

→ **Score = 1:** 0.6% CVA/year

→ **Score ≥ 2:** ≥ 2.2% CVA/year

10. Friberg et al. 2012 Eur Heart J 33:1500-1510.

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OAC Options

- **Warfarin (Coumadin)**
  - Reduce stroke risk by 65%
- **DOACs**
  - Superior stroke prevention than coumadin
  - Lower bleeding risk than coumadin[11]
- **Anti-platelets**
  - Effectiveness debated[12]
  - 19% stroke risk reduction (8 trials, >4,000 patients)

11. Hsu et al. 2018 Clin Pharmacol Ther 104:301-310.
12. Hsu et al. 2016 JACC 67:2913-2923.

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Better Stroke Outcomes with OAC Use

- Stroke severity and in-hospital mortality is reduced for patients receiving therapeutic coumadin or DOAC.[13]

- Lack of OAC is associated with higher risk of:
  - Initial stroke (OR 2.95)
  - Recurrent stroke (OR 2.8)
  - All-cause death (OR 2.75).[14]

13. Xian et al. 2017 JAMA 317:1057-1067.
14. Mazurek et al. 2017 Stroke 48:2198-2205.

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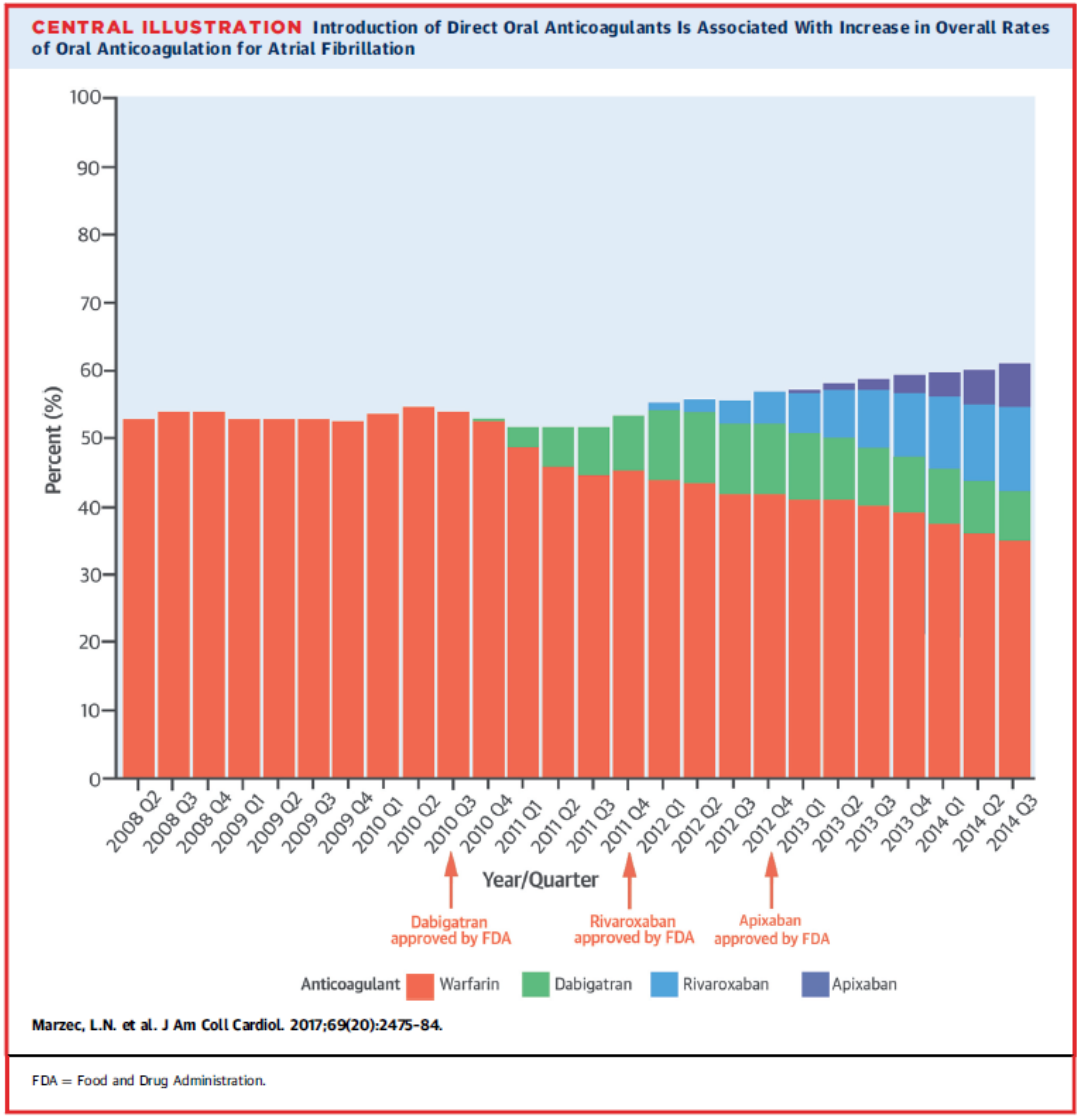
Underutilization of Anticoagulation in the US



15. Marzec et al. 2017 JACC 69:2475-2484.

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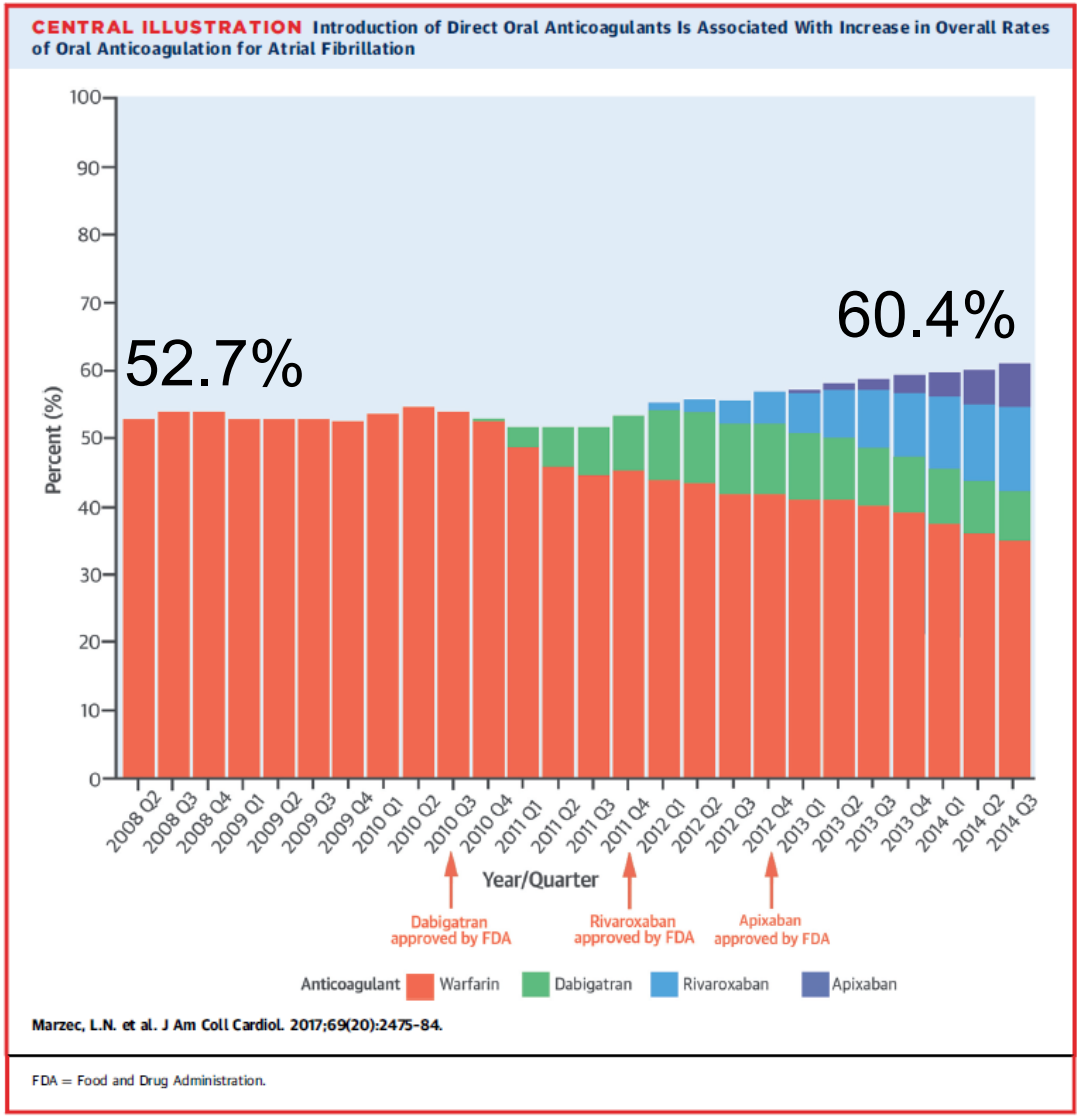

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Reasons for withholding anticoagulant

Bleeding risk associated with OAC use: HAS-BLED score

HTN (+1)
Abnormal liver fxn (+1)
Abnormal renal fxn (+1)
Stroke/TIA (+1)
Bleeding predisposition (+1)
Elderly: Age ≥ 65 (+1)
Drugs (anti-platelet) (+1)
Drugs (alcohol) (+1)

→ **Score 1:** 1% bleed/yr
→ **Score 2:** 1.9% bleed/yr
→ **Score 3:** 3.7% bleed/yr
→ **Score 4:** 8.7% bleed/yr
→ **Score 5:** >10% bleed/yr

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Underutilization of OAC

CHADS-VASC

Congestive heart failure (+1)

HTN (+1)

Age ≥ 65 (+1)

Age ≥ 75 (+1)

Diabetes (+1)

Stroke/TIA (+2)

Sex (female) (+1)

Vascular disease (+1)

HAS-BLED

HTN (+1)

Abnormal liver funct (+1)

Abnormal renal funct (+1)

Stroke/TIA (+1)

Bleeding predisposition (+1)

Elderly: Age ≥ 65 (+1)

Drugs (anti-platelet) (+1)

Drugs (alcohol) (+1)

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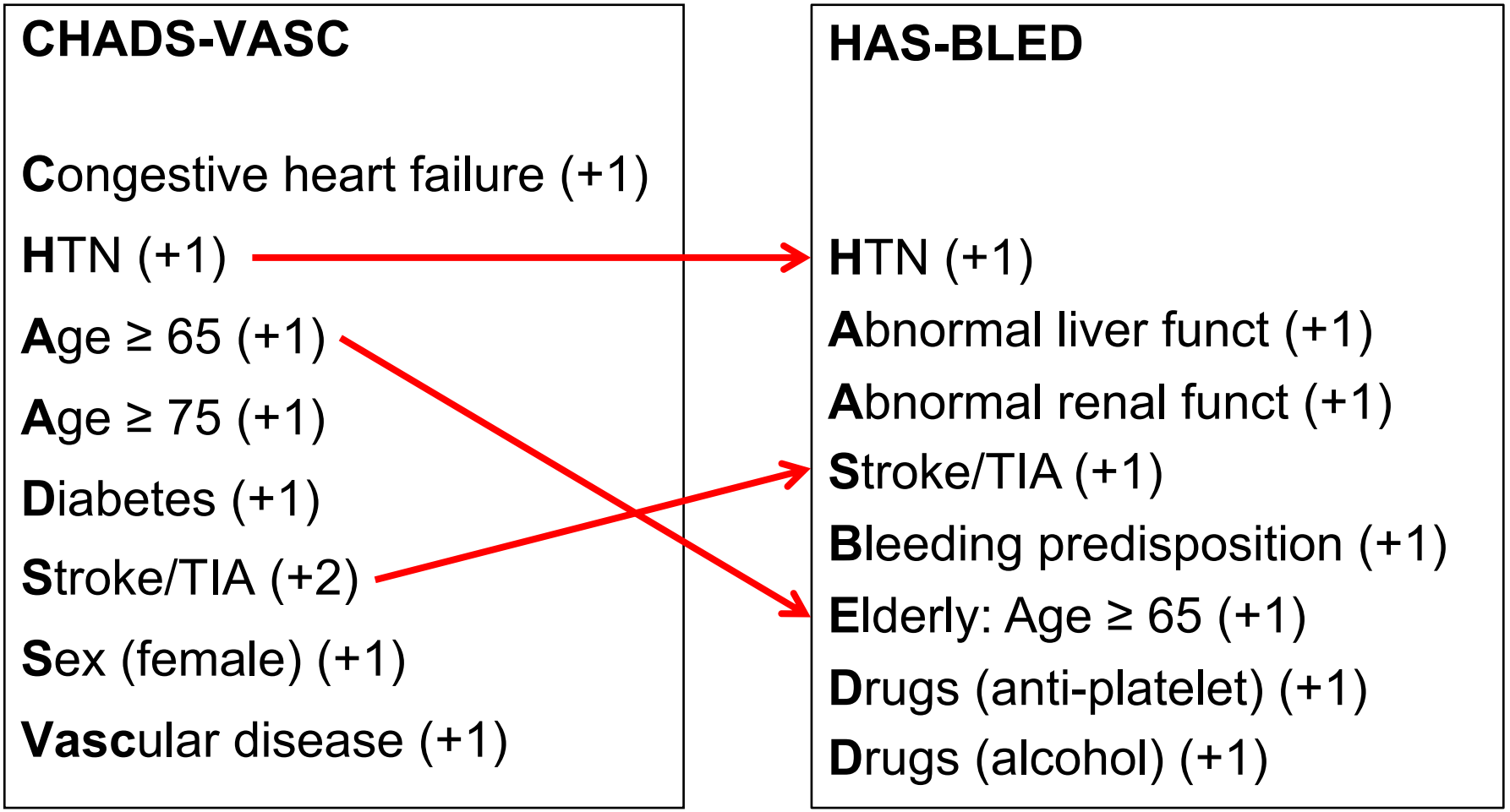
Underutilization of OAC: Stroke Risk and Bleeding Risk Rise Together



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Attempts to Reduce Underutilization of OAC

- Patient and Clinician education efforts
  - IMPACT-AF: international, cluster randomized trial[16]
  - Marginal increase in adherence to anticoagulation guidelines (adherence increase from 68% to 80% at one year)

- Non-reversible risk factors for bleeding[11]
  - History of bleeding, non-reversible substrate
  - Renal impairment
  - Cognitive impairment / dementia / frailty

16. Vinereanu et al. 2017 Lancet 390:1737-1746.
11. Hsu et al. 2018 Clin Pharmacol Ther 104:301-310.

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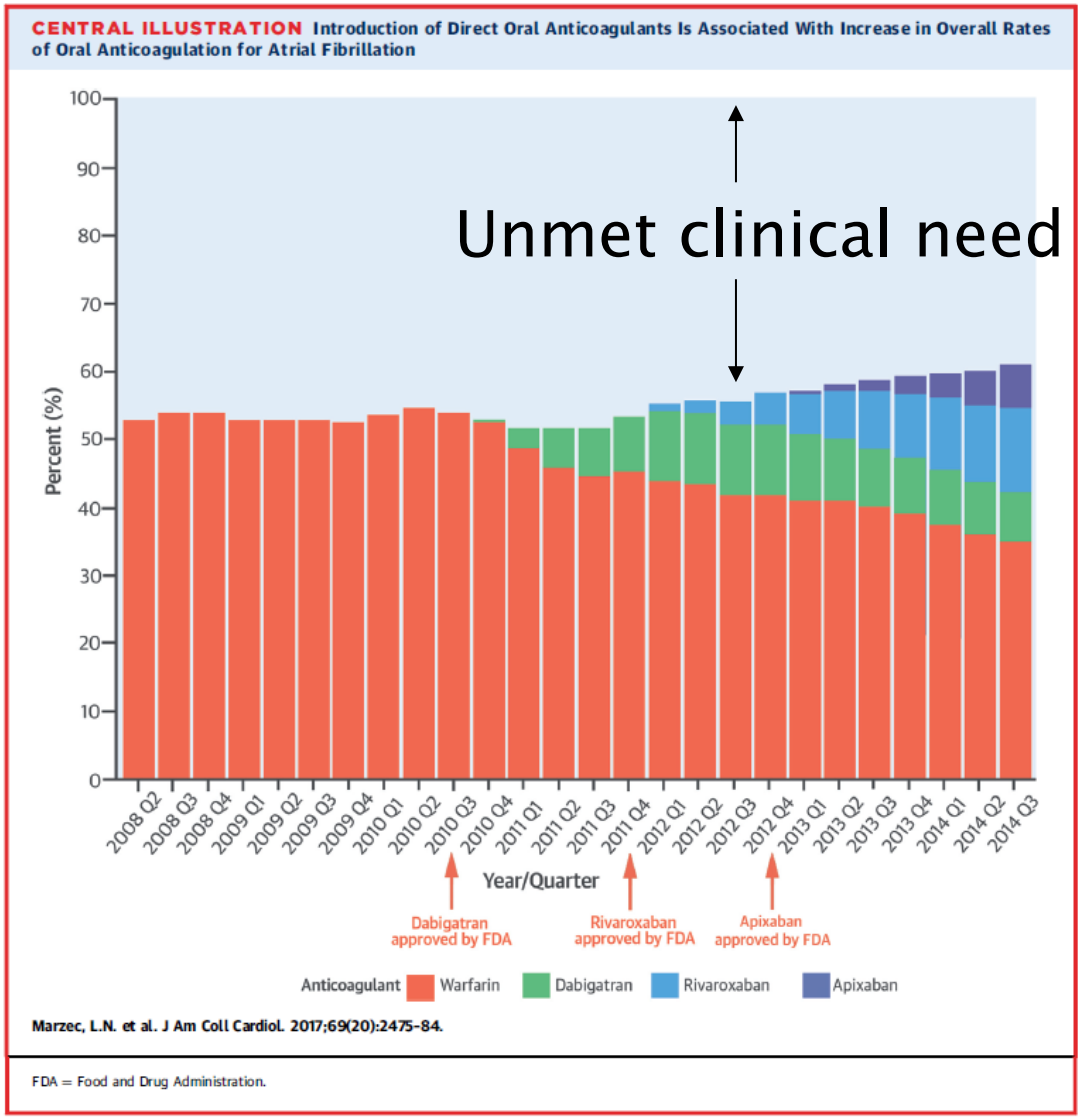

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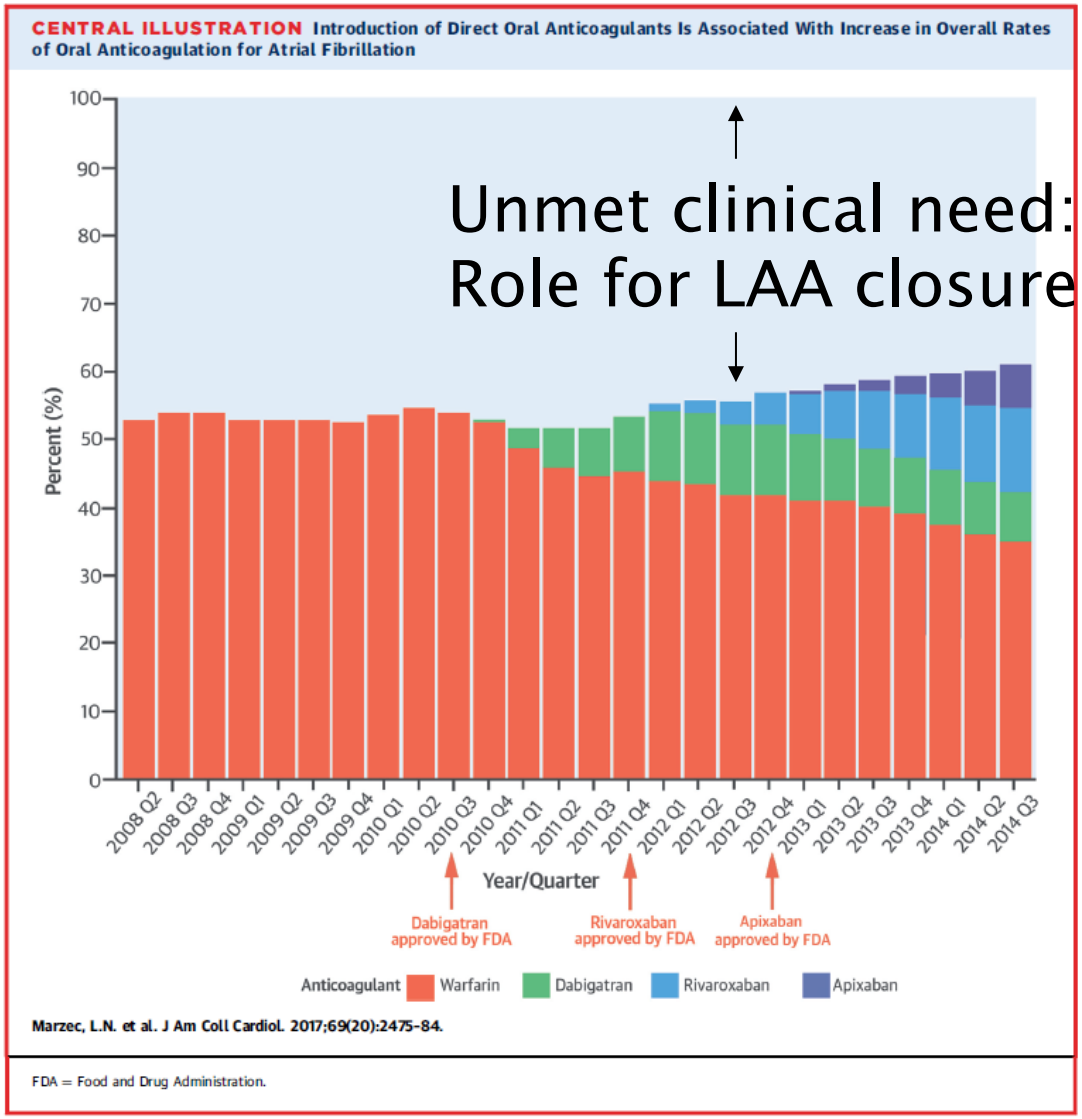

15. Marzec et al. 2017 JACC 69:2475-2484.

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Thrombi that Cause NVAF-Related Stroke Usually Originate in the Left Atrial Appendage

Study	# of patients	Thrombus in LAA	Thrombus in LA cavity
Stoddard et al. 1995 JACC 25:452-459	317	66	1
Manning et al. 1994 Circ 90:1-21a	233	34	1
Aberg et al. 1969 Acta Med Scand 185:373-379	506	35	12
Tsai et al. 1990 J Formosan Med Assoc 89:270-274	52	2	2
Brown et al. 1993 Int J Card Imaging 9:65-72	48	12	1
Manning et al. 1994 Circ 90:1202a	171	8	3
Klein et al. 1994 Circ 90 (Suppl 1):21a	359	19	1
Leung et al. 1994 JACC 24:755-762	272	19	0
Hart et al. 1994 Stroke 25:1337-1341	60	6	0
Total	**1,288**	**201**	**21**

17. Blackshear JL et al. 1996 Ann Thorac Surg 61: 755-759.,
18. Odell JA et al. 1996 Ann Thorac Surg 61: 565-569., 19. Lindsay BD et al. 1996 61: 515.

Thrombi that Cause NVAF-Related Stroke Usually Emanate from the Left Atrial Appendage

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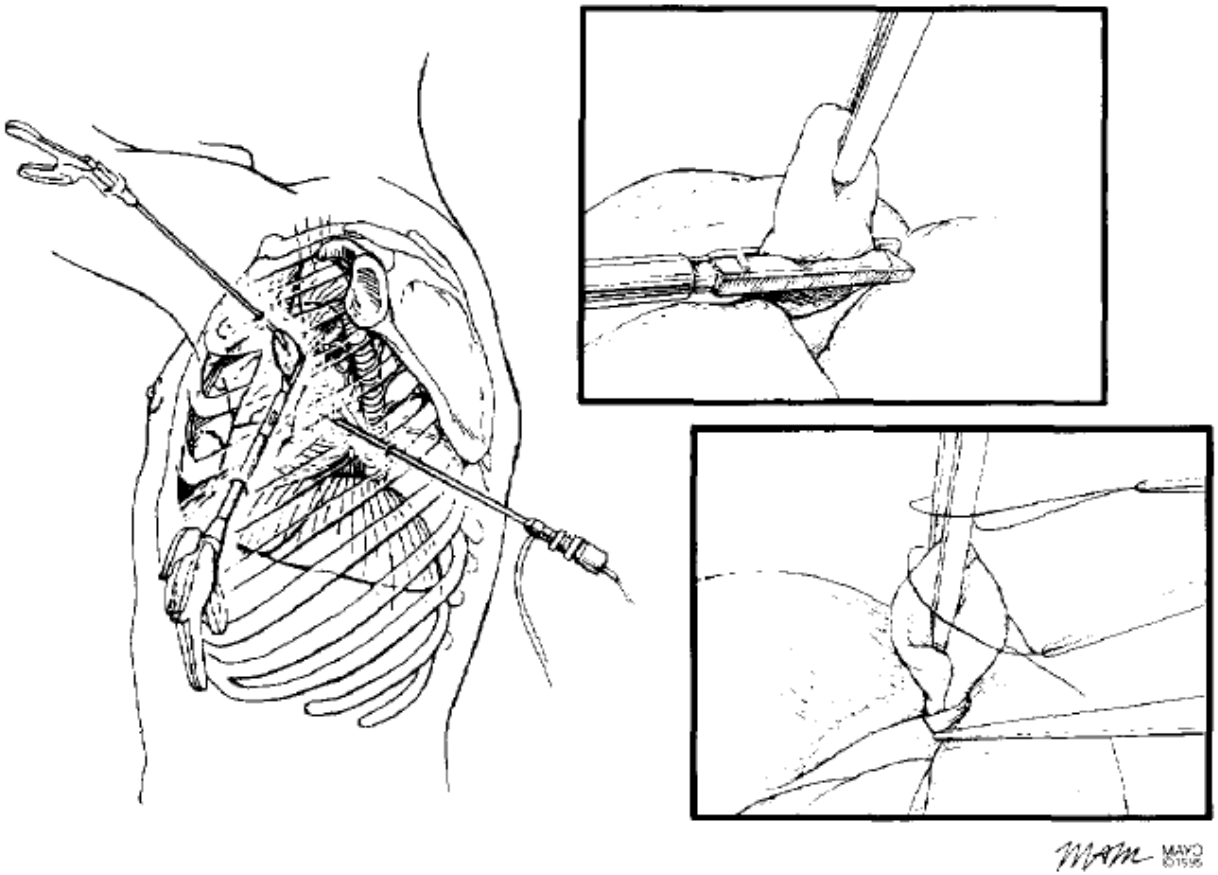
Total	**1,288**	**201 (91%)**	**21**

17. Blackshear JL et al. 1996 Ann Thorac Surg 61: 755-759.,
18. Odell JA et al. 1996 Ann Thorac Surg 61: 565-569., 19. Lindsay BD et al. 1996 61: 515.

LAA Occlusion Proof of Concept



20. Adapted from Odell JA et al. 1996 Ann Thoracic Surg 61:565-56

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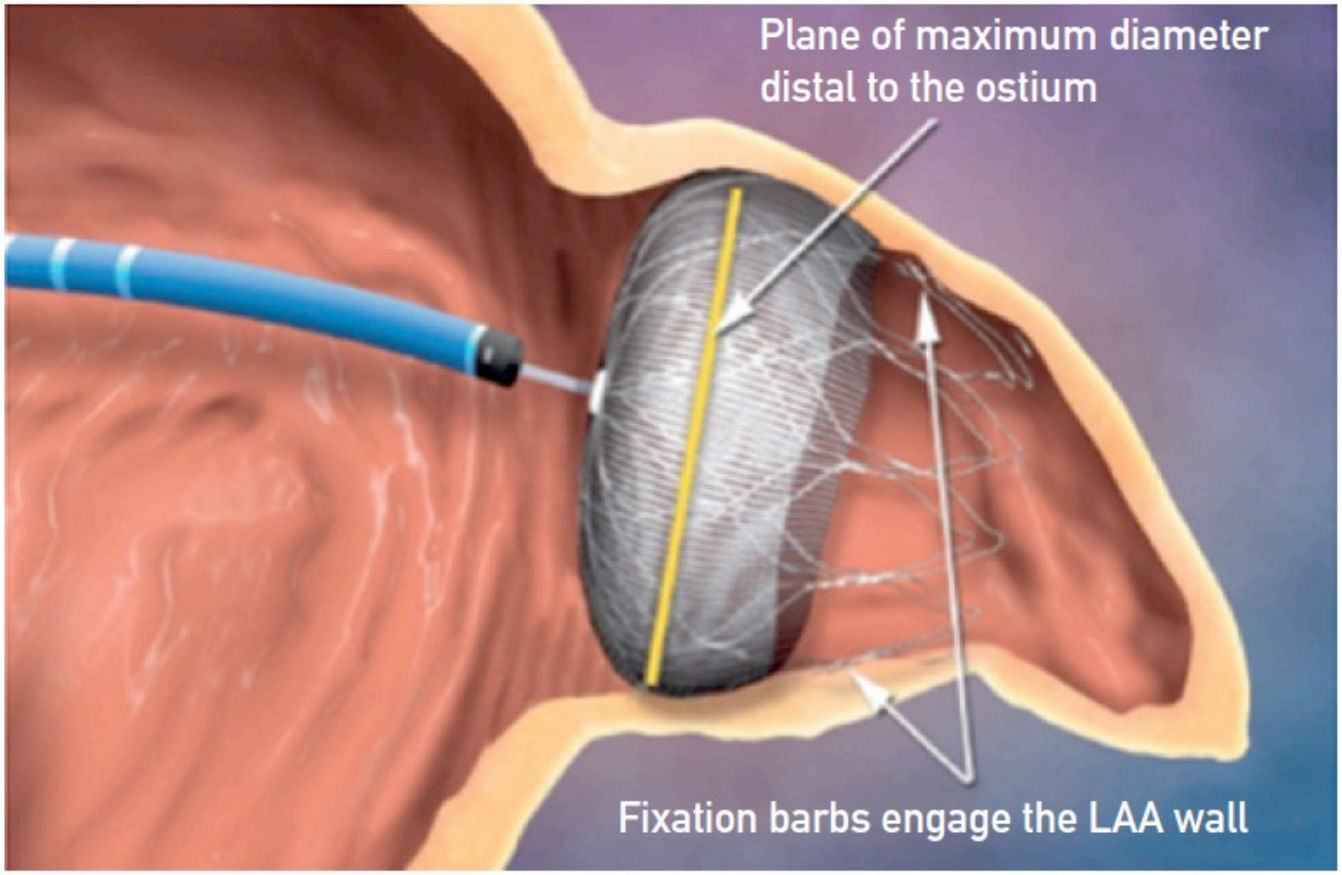
Watchman Device Deployed in the LAA



21. Adapted from Holmes DR et al. 2019 Mayo Clinic Proc 94:864-874.

Watchman Clinical Trials

- **Two Randomized Clinical Trials:**
  - PROTECT AF (NCT00129545)[22]
  - PREVAIL (NCT01182441)[23]
    - Watchman vs. Coumadin, 2:1, goal to assess safety/efficacy
    - For device: aspirin/coumadin 6 wks, aspirin/Plavix 6 mos, then aspirin only if TEE revealed no leak

22. Holmes DR et al. 2009 Lancet 374:534-542.
23. Reddy V et al. 2018 Stroke 49:1464-1470.

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Watchman Clinical Trials

- Meta-analysis of PROTECT-AF and PREVAIL[24]
  - 1114 patients total
  - Composite endpoint (stroke, systemic embolism, or cardiovascular/unexplained death)
  - Similar frequency in the device and coumadin arms:

    HR 0.82, 95% CI 0.58-1.17, p = .27

24. Reddy V et al. 2017 JACC 70:2964-2975.

Watchman Clinical Trials

- Meta-analysis of PROTECT-AF and PREVAIL[24]
  - Reduction in hemorrhagic stroke in device arm
    - HR 0.2, 95% CI 0.07-0.56, P=.002
  - Reduction in death rate in device arm
    - CV, unexplained HR 0.73, 95% CI 0.37-0.94, P=.035
    - All-cause HR 0.48, 95% CI 0.54-0.98, P=.0003

24. Reddy V et al. 2017 JACC 70:2964-2975.

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Watchman Clinical Trials

- Meta-analysis of PROTECT-AF and PREVAIL[24]
  - More ischemic strokes in device arm, but a reduction in disabling or fatal strokes compared with coumadin arm

    (0.44 vs 1.0 per 110 pt/yrs)

24. Reddy V et al. 2017 JACC 70:2964-2975.

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Watchman Outcomes: 5-Year Followup

- Continued Access Registry of PROTECT-AF[25]
  - 566 patients
  - Mean follow-up 52 months
  - Primary safety and efficacy endpoints similar to the main trial

25. Reddy V et al. 2011 Circulation 123:417-424.

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Watchman Procedural Success Rates

TRIAL	PREVAIL	CAP1	CAP2	ASAP	EWO	PAF	WASP
N	265	566	579	150	1019	449	201
Deployment Success Rate	95.1%	94.4%	94.8%	94.7%	98.5%	90.9%	98.5%

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Watchman Implant Safety Considerations

- Large-bore venous catheter
- Trans-septal puncture
- Barbs on device / pericardial effusion
- Device embolization
- Device-associated thrombus

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Watchman Safety

- PROTECT-AF
  - 7% of patients with safety events (pericardial effusion, stroke, or device embolization)
  - 2.7% of patients in Continuous Access Registry with safety events (role for proceduralist experience)

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Adjunctive Therapy

- United States:
  - Patients must take coumadin at least 45 days post procedure
- Europe
  - Patients may be prescribed coumadin, DOAC, or antiplatelet agents post procedure

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Adjunctive Therapy

- United States:
  - Patients must take coumadin at least 45 days post procedure
- Europe
  - Patients may be prescribed coumadin, DOAC, or antiplatelet agents post procedure

Important due to device thrombus noted on ~4% of devices with routine echocardiography.

Further assessment with ongoing, multicenter randomized trial: NCT02928497

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Watchman Approval

- FDA approval (US – based on RCTs)
- CE mark (Europe – based on nonrandomized trials)

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Watchman: Guidelines

- **ACC/AHA/HRS (2019 update):** Class IIb recommendation for AF patients with contraindications to long-term anticoagulation (LOE B-NR)

- **ESC (2016):** Class IIb recommendation (LOE B)

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Cost Effectiveness

- Based on the pivotal trials, LAA occlusion is cost-saving compared with DOACs in 5 years and coumadin in 10 years.[26]
- LAA occlusion is the lowest cost therapy at 5 years (patient out-of-pocket costs).[27]
- LAA occlusion is the lowest cost therapy at 10 years (Medicare).[24]

26. Reddy et al. 2015 JACC 66:2728-2739.
27. Reddy et al. 2017 JACC 70:880.

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Question 3

What is the most appropriate treatment strategy for a 66-year-old woman with persistent AF, HTN, DM2, and rheumatic mitral stenosis who presents with recurrent anemia on coumadin with no bleeding source identified:

1. Watchman implantation.
2. Lariat implantation.
3. Surgical LAA ligation.
4. Continue coumadin.

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Question 4

66-year-old woman with a prior history of paroxysmal AF, HTN, DM2, and who presents with recurrent anemia on eliquis with no bleeding source identified. No AF detected for 1 year.

What is the most appropriate next step in the management?

1. Watchman implantation.
2. Perform ambulatory arrhythmia monitoring to determine if AF is present.
3. Lariat implantation.
4. Surgical LAA ligation.

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Question 4

66-year-old woman with a prior history of paroxysmal AF, HTN, DM2, and who presents with recurrent anemia on eliquis with no bleeding source identified. No AF detected for 1 year.

What is the most appropriate next step in the management?

1. Watchman implantation.
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3. Lariat implantation.
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Incomplete LAA Occlusion

- The LAA orifice is typically oval, and the Watchman device is round, raising the possibility of blood leakage around the device.
- Significant leak has been defined to be 1 to 5mm on TEE.
- Leak > 5mm is considered significant, and is an indication for continuation of OAC.
- Leak closure can also be considered in such cases.[28]

28. Alkhouli et al. 2018 JACC Cardiovasc Interv 11:e83-e85.

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Other LAA Occlusion Devices

- **Endocardial:**
  - Amplatzer Cardiac Plug (ACP)
  - Amulet
- **Epicardial/Surgical:**
  - LARIAT
  - AtriClip

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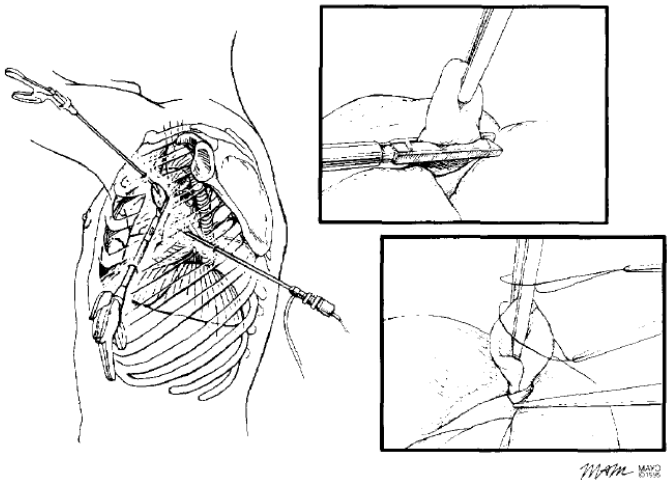
Surgical LAA occlusion

- Surgical LAA occlusion has been described, and is typically performed in the context of other cardiac surgery (e.g., valve surgery, CABG).
- Techniques for closure vary, including oversew of the appendage versus true amputation.



20. Adapted from Odell JA et al. 1996 Ann Thoracic Surg 61:565-569.

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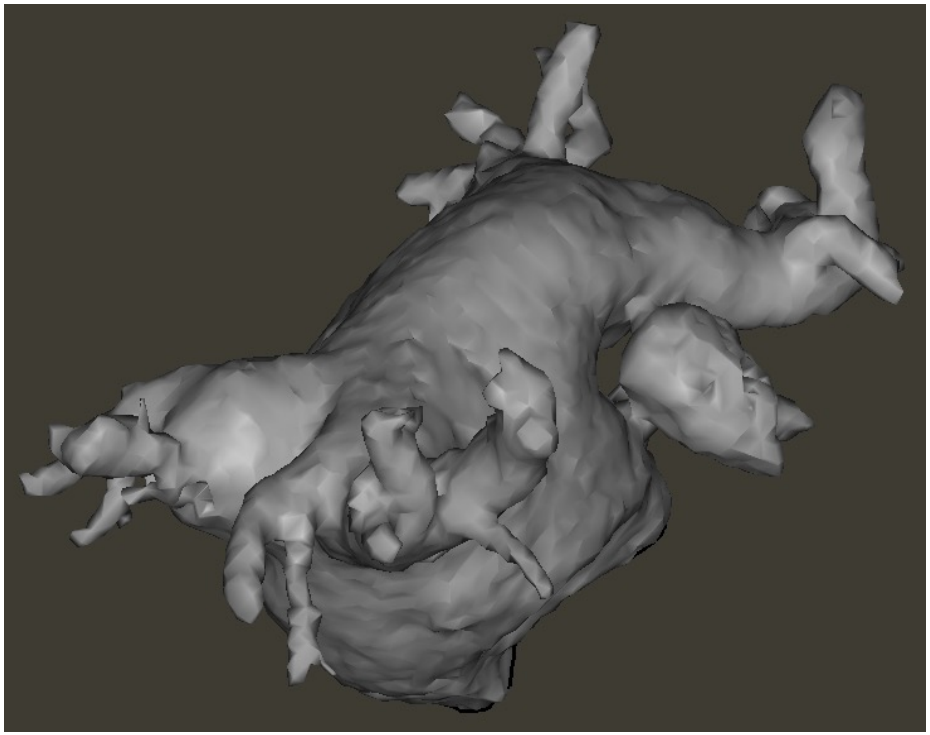
Surgical LAA Occlusion

- Incomplete closure is associated with thromboembolic events.[29]



29. Aryana et al. 2015 Heart Rhythm 12:1431-1437.

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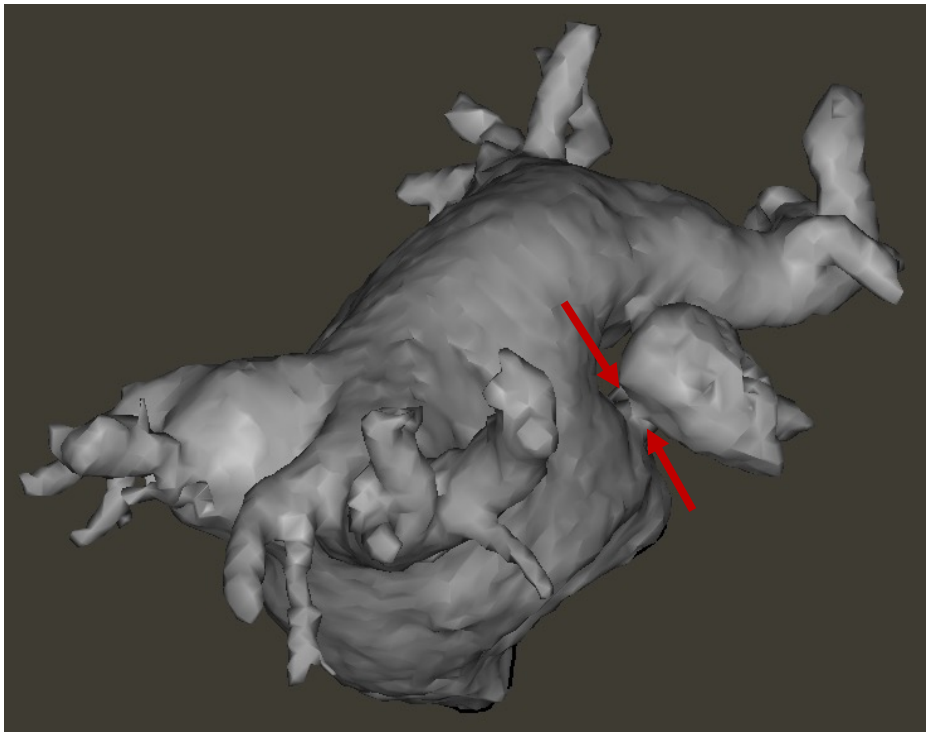

29. Aryana et al. 2015 Heart Rhythm 12:1431-1437.

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Summary

- Oral anticoagulants are the cornerstone for prevention of AF-related strokes. Impact of oral anticoagulants is limited by adverse effects and non-adherence.

- Left atrial appendage occlusion is a feasible alternative to oral anticoagulants for patients who cannot tolerate anticoagulation in the long term.

- Left atrial appendage occlusion can be performed safely. Long-term effectiveness is being evaluated with several studies in progress.

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Thank you for your attention!

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